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ELECTROENCEPHALOGRAPHIC CLASSIFICATION OF EPILEPTIC PATIENTS AND CONTROL SUBJECTS

FREDERIC A. GIBBS, M.D.

ERNA L. GIBBS

AND

WILLIAM G. LENNOX, M.D.

BOSTON

The clinical application of electroencephalography is complicated by the wide range of individual patterns encountered in the most carefully selected control groups and by the fact that almost all patterns which might be used for diagnosis can be found in the electroencephalograms of symptom-free persons.[1] Nevertheless, a relation has been shown between abnormalities in the electroencephalogram and clinical epilepsy, and specific relationships have been reported between different types of clinical seizures and the electroencephalographic patterns that accompany them. It seemed likely that if the routine electroencephalograms of a large group of epileptic patients were compared with those of a large group of nonepileptic subjects, certain wave forms and frequencies would be encountered so rarely among the nonepileptic subjects and so commonly among epileptic subjects that they could be given diagnostic significance. It was also considered possible that differences might appear between the routine electroencephalograms of patients with contrasting types of clinical seizures and that recognition of these differences might lead to a better understanding of the variations in the underlying pathologic physiology of epilepsy and, ultimately, to a more individualized and rational therapy.

MATERIAL

The control group consisted of 1,000 supposedly healthy men and women 20 years of age and over. It contained college students, medical students, hospital employees, members of the hospital staff, school teachers and candidates for military service. No one was included who had a known history of epilepsy or disease of the central nervous system, and all persons were questioned specifically on this point. The group may have contained a few persons who would have been considered abnormal had they been subjected to careful clinical examination; this is unavoidable in such a study and does not seriously detract from the value of the control group.

The total series of epileptic patients studied electroencephalographically numbered 2,805. The first 1,565 patients, however, were not a random sample of an epileptic population, for at the beginning of our studies patients were selected because of the frequency and clearly defined character of their clinical seizures. Furthermore, the instrument used for recording these early

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From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

This study was aided by a grant from the Rockefeller Foundation. Assistance with tabulation of the data was provided by Works Progress Administration Project No. 23321.

1. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

electroencephalograms was somewhat inferior to that employed at present, and, although the major significant features of the records were obvious, it was impossible in all cases to make the fine distinctions required for our present classification. Some statements will be based on the total series of 2,805 epileptic patients, but the comparison of normal and epileptic subjects will be confined to the most recent samples of 1,000 normal adults and 1,260 epileptic patients. The latter group constituted a random sample of private and clinic patients who came to the Boston City Hospital during the years 1938 to Oct. 1, 1942 inclusive. The ages and types of seizures are shown in table 1.

CLINICAL METHOD

Before we go further, it seems advisable to indicate the point of view from which we have approached the problem and to outline the general plan of procedure. The point of view is neither strictly clinical nor strictly electroencephalographic. After much experimentation with the data, it has been found possible to reconcile the evidence from both sources and to organize it so that it makes sense. Only such clinical concepts have been used as seemed definitely advantageous. The clinical data have been reduced to an abbreviated form; they are presented in terms of the clinical diagnosis and the type or types of clinical seizures. These clinical data are

TABLE 1.—*Incidence of Different Types of Clinical Seizures and Combinations of Seizures Among 1,260 Epileptic Patients of Various Ages*

	Clinical Diagnosis															
	Petit Mal		Petit Mal and Grand Mal		Grand Mal		Grand Mal and Psychomotor		Psychomotor		Petit Mal, Grand Mal and Psychomotor		Focal		Total	
Age, Yr.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-4	10	20.0	3	6.0	31	62.0	0	0	1	2.0	0	0	5	10.0	50	100
5-9	26	25.2	12	11.7	46	44.7	3	2.9	6	5.8	1	1.0	9	8.7	103	100
10-14	27	17.1	35	22.2	71	44.9	9	5.7	9	5.7	0	0	7	4.4	158	100
15-19	15	6.8	46	21.1	113	51.6	12	5.5	16	7.3	6	2.7	11	5.0	219	100
20-24	4	2.3	39	22.5	93	53.8	10	5.8	18	10.4	4	2.3	5	2.9	173	100
25-29	6	4.3	18	13.0	79	57.2	14	10.2	12	8.8	5	3.6	4	2.9	138	100
30-34	2	1.9	13	12.1	65	60.7	14	13.1	8	7.5	1	1.0	4	3.7	107	100
35-39	2	2.0	4	4.1	63	64.3	15	15.3	10	10.2	1	1.0	3	3.1	98	100
40-44	1	1.5	3	4.5	42	63.7	8	12.1	7	10.6	0	0	5	7.6	66	100
45-49	0	0	4	7.7	34	65.3	3	5.8	3	5.8	1	1.9	7	13.5	52	100
50-54	0	0	3	6.8	33	75.1	4	9.1	2	4.5	0	0	2	4.5	44	100
55+	0	0	1	2.0	41	78.8	2	3.8	3	5.8	0	0	5	9.6	52	100
Total	93	7.4	181	14.4	711	56.4	94	7.5	95	7.5	19	1.5	67	5.3	1,260	100

compared with the type of electroencephalogram obtained during the routine electroencephalographic examination.

It is important to state at once who made the clinical diagnoses and what classification of clinical seizures was used. For about one third of the patients the diagnosis was made by one of the authors, and for the rest, by other members of the hospital staff or by outside physicians who referred patients for electroencephalographic examinations.

The classification of clinical seizures that was adopted corresponds closely to the tripartite classification that has been in fairly general use for many years; seizures are reported as grand mal, petit mal or psychomotor or as mixtures of these types. The medical community in which we work uses this classification in essentially the same sense that we do. As might be expected, some physicians are more and some are less precise, but we have accepted as final the clinical classification of the physician who made the clinical examination. Our figures do not show the highest correlations obtainable between the clinical and the electroencephalographic data; they indicate merely the correlation that was obtained from a more or less routine sample of diagnostic opinion in our community.

It is important that the reader understand the grounds on which we, and most of the physicians sending patients to us, classify the three main types of seizures.

Petit mal is used in a restricted sense to mean a transient lapse of consciousness (usually five to twenty seconds) without tonic spasm; if convulsive movements are present, they consist of rhythmic, approximately 3 per second clonic jerkings of the eyelids, head or arms. This type of seizure is sometimes referred to as pyknolepsy or, better, pyknoepilepsy. Some clinicians have applied the term petit mal to any form of seizure which is short or mild. When used in this way the term lacks specific meaning; it refers not to the type but to the severity of the seizure. Such a use of the word obstructs discussion of the subject. A psychomotor seizure is a period of impaired consciousness or amnesia with apparently purposeful movements, sometimes accompanied by manifestations of emotional excitement, particularly fear or rage. A grand mal seizure is a tonic-clonic convulsion. In some cases seizures are of a mixed type, and in other cases, although the seizures are of a pure type, more than one type of seizure is present.

This classification has no claims to exclusive validity. Much can be said in favor of other systems—for example, those based on etiologic factors or on the anatomic structures involved. We have used this classification because it seems simple and natural, it is more or less tacitly accepted by a large number of neurologists and, last but most important, it brings into orderly relation a great mass of clinical, electroencephalographic and chemical data.[2]

ELECTROENCEPHALOGRAPHIC METHOD

Recording.—In all cases the electrical activity over the left and right frontal, parietal and occipital cortex was recorded with monopolar leads (with the indifferent electrode on both ear lobes). A Grass electroencephalograph was used to register the activity of at least three areas simultaneously. Records were taken with the subject seated and the eyes closed. Fifteen minutes of activity was recorded during rest, then two minutes during moderate overventilation and three minutes during recovery.

Interpretation and Classification.—The electrical activity of the cortex is so complex that if it is to be considered at all, it must be simplified. If it is simplified, there is the risk that its most significant aspects will be disregarded. Before the present classification was adopted, the electrical activity of the cortex was studied over a wide range of clinical conditions. Different types of integration and weighting were experimented with. Finally, the particular integration and weighting which gave the maximum discrimination between normal and abnormal neurologic states was adopted. The classification is necessarily based on subjective criteria, because only an exceedingly cumbersome objective method can integrate and weight the many significant aspects of the electroencephalogram, such as frequency, amplitude, wave form, variability and extent of cortex involved. The classification is empiric; it has been adjusted arbitrarily to give the maximum differentiation between different clinical conditions and different states of cerebral activity.

CLASSIFICATION OF ADULT ELECTROENCEPHALOGRAMS[3]

The classification is based primarily on frequency and wave form, although amplitude is taken into account. Focal disorders are considered under a separate heading. The various categories that are used are listed in the order of frequency of the waves—slow first and fast last. A sample record from each category is shown in figure 1. When the categories that are classified as paroxysmal are con-

2. (*a*) Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations in the Carbon Dioxide Content of the Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223-239 (Feb.) 1940. (*b*) Nims, L. F.; Gibbs, E. L.; Lennox, W. G.; Gibbs, F. A., and Williams, D.: Adjustment of Acid-Base Balance of Patients with Petit Mal Epilepsy to Overventilation, Arch. Neurol. & Psychiat. **43**: 262-269 (Feb.) 1940.

3. It should not be supposed that after having read this outline a competent electroencephalographer would be able to classify records in a manner identical with that used in our laboratory. The discriminations required are much like those needed in classification of tumors of the glioma group. Neither verbal descriptions nor representative samples are adequate. In order to learn to use the classification in our sense, it is necessary to attempt to duplicate the classification of a large number of records.

sidered individually, they are placed at the fast or the slow extreme, depending on the frequency of the waves that form the paroxysm. In the description which follows, however, and in some later figures, all paroxysmal categories are grouped together. The position of the class referred to as *low voltage fast* may appear to be inconsistent, but our experience indicates that frequency of the discharge is intermediate between 10½ and 11 per second.

A. Paroxysmal (Parox.).—This category includes all records in which clearly evident seizure discharges of high voltage waves of a distinctive pattern are present in any lead. It is subdivided as follows:

1. Petit Mal Variant (*P. M. V.*): Two per second alternating wave and spike pattern.

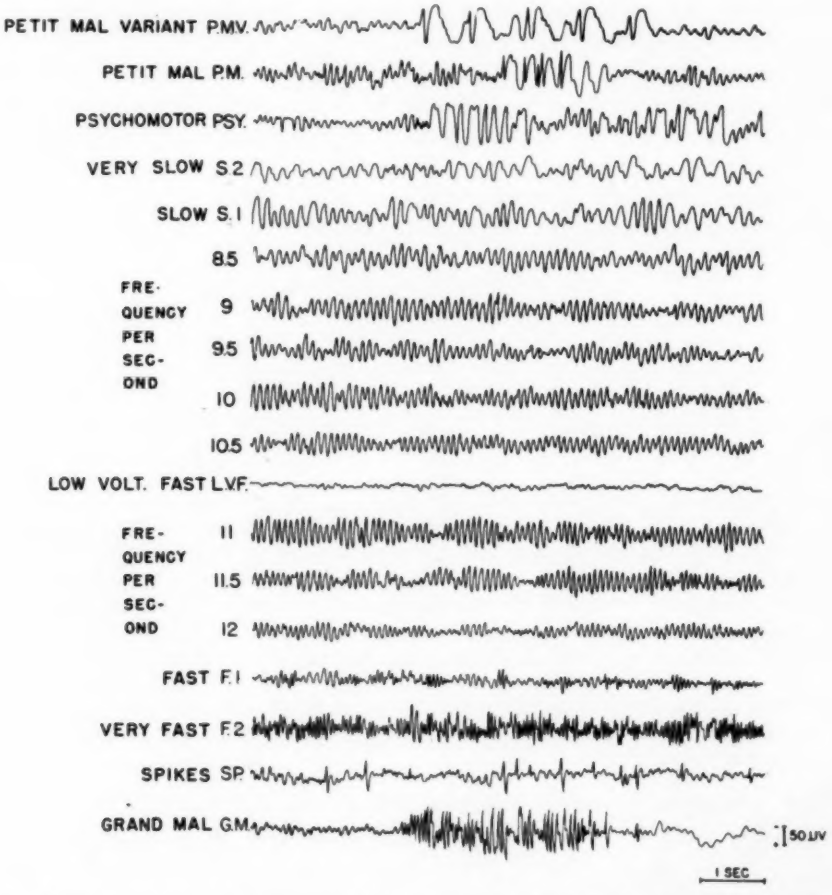

Fig. 1.—Sample strips of electroencephalograms, illustrating the characteristic features of the record in each electroencephalographic category. At the left of each strip is the abbreviation for the category. A description of the classification is given in the text. Tracings are approximately one-fourth actual size. At the right lower corner is the calibration for 50 microvolts and for one second.

2. Petit Mal Type (*P. M.*): Three per second alternating wave and spike pattern, i. e., the pattern which occurs during a clinical petit mal seizure.

3. Psychomotor Type (*Psy.*): Discharges of flat-topped 4 per second waves, together with high voltage 6 per second waves or discharges of irregular positive spikes, appearing in a record previously relatively free from such activity, i. e., the pattern which occurs in a clinical psychomotor seizure.

4. Grand May Type (*G.M.*): Discharges of fast waves (12 to 35 per second) of increasing amplitude, i. e., the pattern which occurs in a clinical grand mal attack. If the voltage is below 50 microvolts, the discharge must last longer than three seconds; if above 50 microvolts, it must last longer than one second, and it must appear in a record previously relatively free from such activity. When the dominant rhythm is continuously fast or when frequently repeated bursts of fast activity occur without change of voltage, the record is classified as fast.

5. Spikes (*Sp.*): Widely separated single or multiple, positive, negative or diphasic spikes. A record which shows discharges of spikes lasting more than one second is classified as fast or as grand mal, depending on the voltage and the duration of the discharge and on whether it is more or less continuous.

B. Slow Activity.—1. Very slow (*S. 2*): Great amount of activity slower than 8 per second in any lead. The amount is considered in terms of the amplitude and the frequency of this activity, the percentage of time it is present and the number of leads in which it appears.

2. Slightly Slow (*S. 1*): Moderate amount of activity slower than 8½ per second in any lead. The amount is considered in terms of the amplitude and the frequency of this activity, the percentage of time it is present and the number of leads in which it appears. A record which contains a mixture of fast and slow waves is classified according to whichever predominates.

C. Normal Activity.—1. From 8½ to 12 per second: The dominant activity is not slower than 8½ or faster than 12 a second. There are no seizure discharges and no significant fast or slow activity. When the frequency varies from lead to lead or from time to time, the record is classified according to whatever frequency predominates.

2. Low Voltage Fast (*L. V. F.*): Low amplitude activity (usually below 20 microvolts), with no countable frequency. The waves which can be seen are predominantly fast.

D. Fast.—1. Slightly Fast (*F. 1*): Moderate amount of activity faster than 12 per second. The amount is considered in terms of amplitude and frequency of the fast activity, the percentage of time it is present and the number of leads in which it appears.

2. Very Fast (*F. 2*): Large amount of activity faster than 12 per second. The amount is considered in terms of the amplitude and frequency of the activity, the percentage of time it is present and the number of leads in which it appears. When the record shows a mixture of fast and slow activity, it is classified according to whichever predominates.

It should be noted that, with the exception of the paroxysmal categories, this classification applies only to young and middle-aged adults. Adjustments are necessary in the slow, fast and normal categories if this classification is to be applied to children or to aged adults. Such adjustments are too complex to be described in the present report. They will be made the subject of a later communication.

Thus far, no definite statement has been made regarding the provisions for classifying localized abnormalities. In actual practice, the presence or absence of a focal abnormality is always noted, and a primary division is made on this basis. If no focus is found, the report is written on a blank headed "Nonfocal Electroencephalogram." Such a report includes a brief description of the record, its classification (as outlined here) and the clinical implications. If a focus is found, the report is written on a blank headed "Focal Electroencephalogram" and includes a statement of the location of the focus, the character of the abnormal

pattern, its classification (as outlined here) and a note on the clinical implications. In the present article, for purposes of simplification, differences in the specific areas involved by a given abnormality are not taken into account; electroencephalograms are considered in terms of frequency, amplitude and wave form, without regard to anatomic distribution. Fifteen per cent of the recent series of 1,260 epileptic patients showed focal abnormalities; their cases are given detailed consideration in a separate article.[4]

RATIONALE OF THE ELECTROENCEPHALOGRAPHIC TERMINOLOGY

Of the 18 tracings reproduced in figure 1, 14 bear labels which are purely descriptive. These types of electroencephalograms, with 1 exception, are nonspecific; i. e., they are not characteristic of any special mental state or any special clinical condition. The exception is the type of record labeled *spikes;* this is just as specific for epilepsy as are the tracing for the petit mal variant and the other three tracings that are given names corresponding to the three principal types of clinical epileptic seizures—petit mal, psychomotor and grand mal. These clinical terms are used in describing electrical records for the following reasons:

During a typical clinical petit mal seizure the electroencephalogram shows high voltage alternate waves and spikes which recur at the rate of approximately 3 per second; during a clinical grand mal seizure, the record shows fast waves of increased amplitude, and during a clinical psychomotor seizure the record shows high voltage 4 to 6 per second waves, many of which have flat tops.[5]

It is more accurate to apply to a particular electroencephalographic pattern the name of the clinical type of seizure with which it is associated than to use a purely descriptive term, for such a term cannot be adequately descriptive, and will therefore be easily misinterpreted. In the present terminology this difficulty is avoided by making reference to a readily available physiologic standard, namely, the electroencephalographic pattern that appears during a given type of clinical seizure.

Since there is a consistent relation between a certain type of clinical seizure and a certain type of paroxysmal electrical discharge, it is not only accurate but useful to connect the phenomena verbally and to speak of petit mal, grand mal and psychomotor types of discharges. This is accepted practice in other fields. The electrocardiographer translates what he sees on his tracings directly into clinical terms. He reports, for instance, that the electrocardiogram shows extrasystoles, experience having proved to him that a certain pattern is the electrical equivalent of a premature heart beat. The first electrocardiologist who spoke in this manner was doubtless reproached for his improper use of language, it being generally agreed that a heart beat by definition is mechanical.

There can be no question of the propriety of speaking of a petit mal type of dysrhythmia when it occurs during a clinical petit mal seizure. Moreover, the roentgenologist refers confidently to a line of reduced opacity as a "fracture" even in the absence of clinical evidence of a break. We believe that it is equally proper to speak of a petit mal type of dysrhythmia when the same pattern appears in a routine record in the absence of clinically obvious seizures, even if the particular patient has no history of petit mal or of epilepsy. This belief is based on the prevalence of the wave and spike formation in the records of persons with a history of petit mal and its

4. Gibbs, E. L.; Merritt, H. H., and Gibbs, F. A.: Electroencephalographic Foci Associated with Epilepsy, Arch. Neurol. & Psychiat. **49**:793-801 (June) 1943.

5. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

rarity in persons without such a history. What is said about the petit mal pattern applies also to the psychomotor and the grand mal pattern.

RESULTS

Epileptic Adults.—The classification previously outlined was applied to the epileptic and to the control group. The results for all epileptic patients appear in the last column of table 2. The distributions for 1,000 controls, 20 years of age and over, and for 730 adult epileptic patients are shown in figures 2 and 3.

TABLE 2.—*Incidence of Various Types of Routine Electroencephalograms Among 1,260 Patients with Certain Types of Clinical Seizures or Combination of Seizures*

Type of Discharge in Routine Electroencephalogram	Clinical Diagnosis: Petit Mal		Petit Mal and Grand Mal		Grand Mal		Grand Mal and Psychomotor		Psychomotor		Petit Mal, Grand Mal and Psychomotor		Focal		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Petit mal variant	3	3.2	11	6.1	20	2.8	1	1.1	0	0	0	0	5	7.5	40	3.2
Petit mal	76	81.6	118	65.1	43	6.0	1	1.1	2	2.1	6	31.6	0	0	246	19.5
Psychomotor	1	1.1	4	2.2	9	1.3	41	43.5	40	42.1	3	15.8	1	1.5	99	7.9
Very slow	2	2.2	8	4.4	119	16.7	13	13.8	6	6.3	2	10.5	20	29.8	170	13.5
Slow	1	1.1	11	6.1	160	22.5	9	9.6	19	20.0	3	15.8	6	9.0	209	16.6
Normal	7	7.5	8	4.4	128	18.0	4	4.3	14	14.7	1	5.3	2	3.0	164	13.0
Fast	2	2.2	7	3.9	121	17.0	16	17.0	6	6.3	0	0	1	1.5	153	12.0
Very fast	0	0	2	1.2	62	8.7	3	3.2	3	3.2	0	0	8	11.9	79	6.3
Spikes	1	1.1	4	2.2	36	5.1	5	5.3	5	5.3	2	10.5	22	32.8	74	5.9
Grand mal	0	0	8	4.4	13	1.9	1	1.1	0	0	2	10.5	2	3.0	26	2.1
Total	93	100	181	100	711	100	94	100	95	100	19	100	67	100	1,260	100

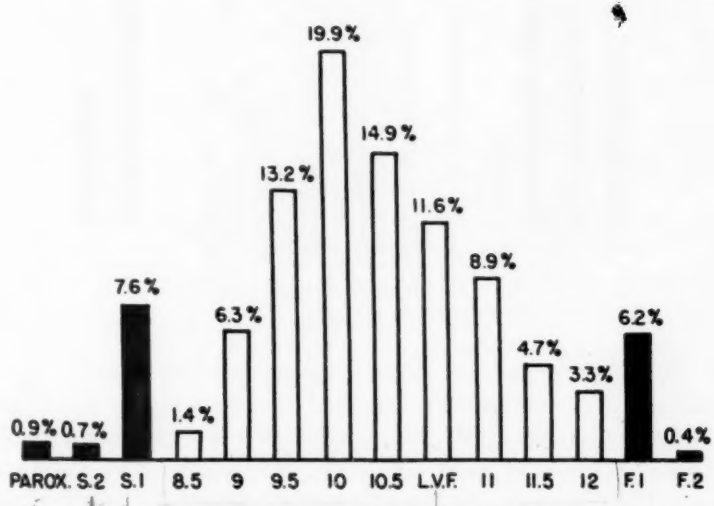

Fig. 2.—Percentage distribution of electroencephalographic types for 1,000 adult controls. The abbreviations at the bottom are the same as those in figure 1, except that "paroxysmal" includes the various seizure discharges, the first three and the last two strips in figure 1. Categories shown in black are considered abnormal. The numbers indicate the percentages of the total series.

The simple population distribution for the controls contrasts with the bimodal distribution for the epileptic patients. The maximum difference between the controls and the epileptic patients is found in the paroxysmal category, and the next greatest difference, in the very slow and very fast categories. Records classified as paroxysmal (*P. M. V., P. M., Psy., Sp.* and *G. M.;* fig. 1 and classification in text) were thirty-three times as numerous among the adult epileptic

patients as among the controls; records in the very fast and very slow categories (*F. 2* and *S. 2*) were twenty times as numerous, and records in the moderately fast and moderately slow categories (*F. 1* and *S. 1*) were two and two-tenths times as numerous.

Bodily characteristics that exhibit a wide range of variation even under standard conditions can be described as "normal" or "abnormal" only in a very coarse sense. The limits of normal are necessarily arbitrary. Argument over these limits is unprofitable. What is important is that clear, reproducible distinctions be made and a precise comparison with adequate control groups furnished. Characteristics that are of borderline normality have less clinical significance than characteristics that are very abnormal. For example, a resting heart rate of 100 beats a minute may be called "abnormal" but is encountered so frequently in healthy persons that it receives little attention. On the other hand, a really extreme tachycardia or an absolute arrhythmia of the heart commands immediate and anxious attention. We have considered the paroxysmal, and also the very

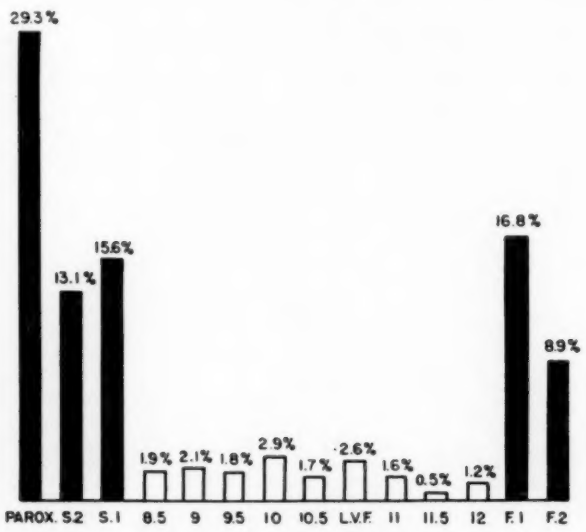

Fig. 3.—Percentage distribution of electroencephalographic types for 730 adult epileptic patients. The symbols are the same as those in figure 2.

slow and the very fast, types of electroencephalograms (*Parox., S. 2, F. 2*) as very abnormal and the moderately slow and the moderately fast types (*S. 1* and *F. 1*) as slightly abnormal. The latter were twice as common in the group of epileptic patients as in the controls, and we believe that they are clinically significant, though obviously far less so than paroxysmal discharges, which occurred thirty-three times as frequently among the adult epileptic subjects as among the controls. The percentages involved are shown in figures 2 and 3 and in table 4.

Variation in the electroencephalograms with age is generally recognized as an exceedingly important factor in the younger age groups,[1] but our unpublished data indicate that it is also important in adults, particularly after the sixtieth year. Separate standards will be needed for the later decades of life, for in these years there is an increased incidence of abnormal electroencephalograms. Much confusion is likely to arise if persons over 60 are judged by the same standards as persons between 20 and 45 years of age.

Epileptic Children.—The greater incidence of abnormalities in the electroencephalograms of young epileptic patients has been remarked on by Walter and

associates,[6] Liberson and Strauss,[7] Robinson [8] and Finley and Dynes.[9] The high incidence of the petit mal wave and spike pattern in children (table 1) and its rarity in adults are in accord with the clinical observation that clinical petit mal seizures tend to disappear in adult life.[10] In the present series, it is interesting to note (table 1) that 84 per cent of the patients with clinical petit mal seizures alone were below 20 years of age, whereas only 37 and 34 per cent of those with clinical grand mal and psychomotor seizures alone were below this age.

In figure 4 the electroencephalographic distribution for 530 epileptic patients 19 years of age or younger is compared with the distribution for 730 patients 20 years of age or over; the actual percentages and ratios are shown in table 4. Nonparoxysmal electroencephalographic abnormalities in adults and children cannot be compared unless special adjustments are made for age. In this figure, therefore, and in the corresponding table (fig. 4 and table 4), and also in figure 7 and tables 2 and 3, the required adjustments were made for age; i. e.,

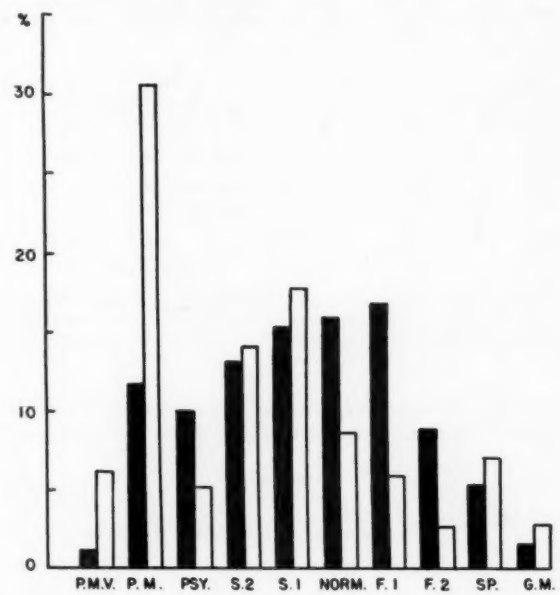

Fig. 4.—Percentage distribution of electroencephalographic types for 530 epileptic patients below 20 years of age (open columns) and for 730 patients 20 years or over (black columns). Numerical data appear in table 4. Categories are adjusted for age.

a record classified as showing moderately slow activity for a 6 year old child was slower than one classified as showing moderately slow activity for a 25 year old man. However, seizure discharges (*P. M. V.*, *P. M.*, *Psy.*, *Sp.* and *G. M.*) do not have to be adjusted for age; they are very abnormal at any age.

6. Golla, F.; Graham, S., and Walter, W. G.: The Electroencephalogram in Epilepsy, J. Ment. Sc. **83**:137-155, 1937.

7. Liberson, W. T., and Strauss, H.: Electroencephalographic Studies: Slow Activity During Hyperventilation in Relation to Age, Proc. Soc. Exper. Biol. & Med. **48**:674-676, 1941.

8. Robinson, L. J.: Incidence of Abnormal Electroencephalogram in Epileptic Persons Over Forty Years of Age, Dis. Nerv. System **2**:55-58, 1941.

9. Finley, K. H., and Dynes, J. B.: Electroencephalographic Studies in Epilepsy: A Critical Analysis, Brain **65**:256-265, 1942.

10. Lennox, W. G.: Science and Seizures: New Light on Epilepsy and Migraine, New York, Paul B. Hoeber, Inc., 1941.

Certain types of seizure discharges appear more commonly in the routine electroencephalograms of epileptic children than in those of epileptic adults; the petit mal variant is five and one-half times, the petit mal type two and six-tenths times and the grand mal type one and nine-tenths times as common in the records of epileptic children as in those of adults. On the other hand, the psychomotor type of seizure discharge and normal rhythms occur twice as often in the records of epileptic adults, and dominant fast frequencies three times as often (last column of table 4).

TABLE 3.—*Relation Between the Clinical Diagnosis and the Routine Electroencephalogram for 1,260 Epileptic Patients and 1,000 Controls* *

Electroencephalographic Diagnosis	Clinical Diagnosis								
	Petit Mal Only, %	Petit Mal and Grand Mal, %	Grand Mal Only, %	Grand Mal and Psychomotor %	Psychomotor %	Petit Mal, Grand Mal and Psychomotor %	Focal, %	Total Number of Epileptic Patients, %	Control Group, %
Clinical and electroencephalographic diagnosis in agreement †	85	76	1	45	42	58	87	87	84
All paroxysmal types	87	80	17.1	52.1	49.5	68.4	44.8	38.6	0.9
Very slow or very fast (S. 2 or F. 2)	2.2	5.6	25.4	17.0	9.5	10.5	41.7	19.8	1.1
Slightly slow or slightly fast (S. 1 or F. 1)	3.3	10.0	39.5	26.6	26.3	15.8	10.5	28.6	13.8
Normal	7.5	4.4	18.0	4.3	14.7	5.3	3.0	13.0	84.2
Total	100	100	100	100	100	100	100	100	100

* This table is a condensation of table 2.
† For patients having two or more types of seizure, the clinical and electroencephalographic diagnoses were considered to be in agreement if the electroencephalographic classification coincided with either of the clinical diagnoses. The electroencephalographic group of petit mal includes the variant type.

TABLE 4.—*Distribution of Electroencephalographic Types Among Epileptic Children and Adults*

Electroencephalographic Classification	Children (0 to 19 Years)		Adults (20 to 70 Years)		Number of Children to One Adult (per 100 of Each)
	Number	Percentage	Number	Percentage	
Petit mal variant	32	6.0	8	1.1	5.5
Petit mal	161	30.4	85	11.6	2.6
Psychomotor	27	5.1	72	10.0	0.5
Very slow *	74	14.0	96	13.1	1.1
Slightly slow *	95	17.9	114	15.6	1.1
Slightly fast *	30	5.7	123	16.8	0.3
Very fast *	14	2.6	65	8.9	0.3
Spikes	37	7.0	37	5.1	1.4
Grand mal	15	2.8	11	1.5	1.9
Normal	45	8.5	119	16.3	0.5
Total number	530	100.0	730	100.0	1.0

* Adjusted for age.

Epileptic Patients of All Ages.—In order to determine at what age petit mal is most common and whether there is a parallelism between the clinical and the electroencephalographic evidence of petit mal, we determined the percentage of patients in the various age groups who had a history, past or present, of clinical petit mal, with or without other types of seizures, and the percentage in each age group who showed the 3 per second wave and spike pattern of petit mal in their routine electroencephalograms. The results of this computation, shown in figure 5, demonstrate that clinical petit mal seizures and wave and spike formations are most frequent in patients less than 20 years of age, after which the incidence of both decreases sharply. A similar comparison was made between clinically diag-

nosed psychomotor seizures and the occurrence of the psychomotor type of seizure discharge in the routine electroencephalogram (fig. 6). The incidence of both clinical and electroencephalographic evidence of psychomotor disorder rose with increasing years up to the age of 40. The incidence of patterns of the psychomotor

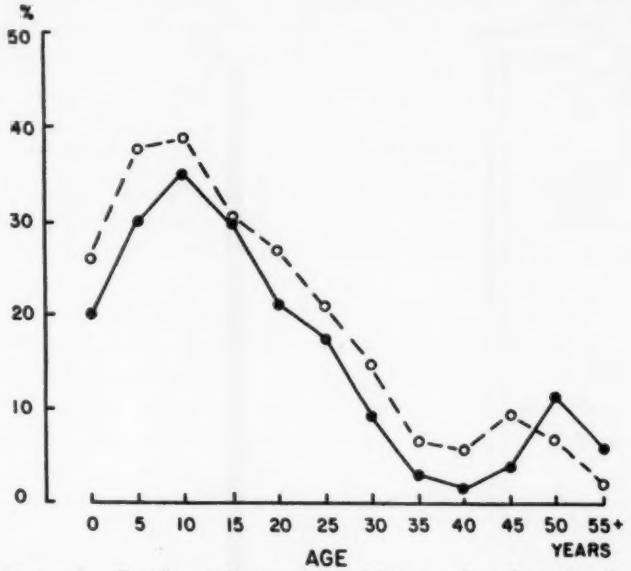

Fig. 5.—Percentage of epileptic patients with a history of petit mal seizures (broken line) and percentage of patients with electroencephalograms showing a wave and spike discharge (solid line) in each age group. Percentages are calculated on the basis of the total number of patients in a given age group (table 1).

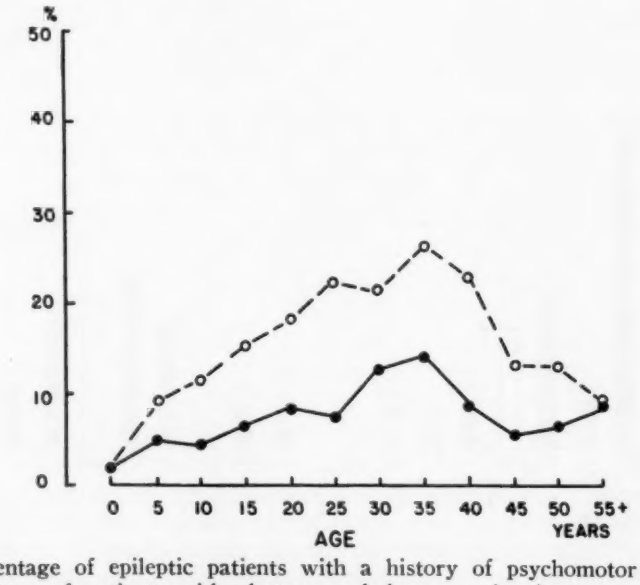

Fig. 6.—Percentage of epileptic patients with a history of psychomotor seizures (broken line) and percentage of patients with electroencephalograms showing a psychomotor type of discharge (solid line) in each age group. Percentages are calculated on the basis of the total number of patients in a given age group (table 1).

type was, however, approximately half the incidence of clinical seizures of this type. Because of the small number of patients showing seizure discharges of the grand mal type, curves for the incidence of such discharges could not be drawn.

Table 2 gives the distribution of types of electroencephalograms for patients of all ages whose disorder on clinical grounds had been diagnosed as a given type, or as a combination of types, of seizures; slow, normal and fast categories were adjusted for age.

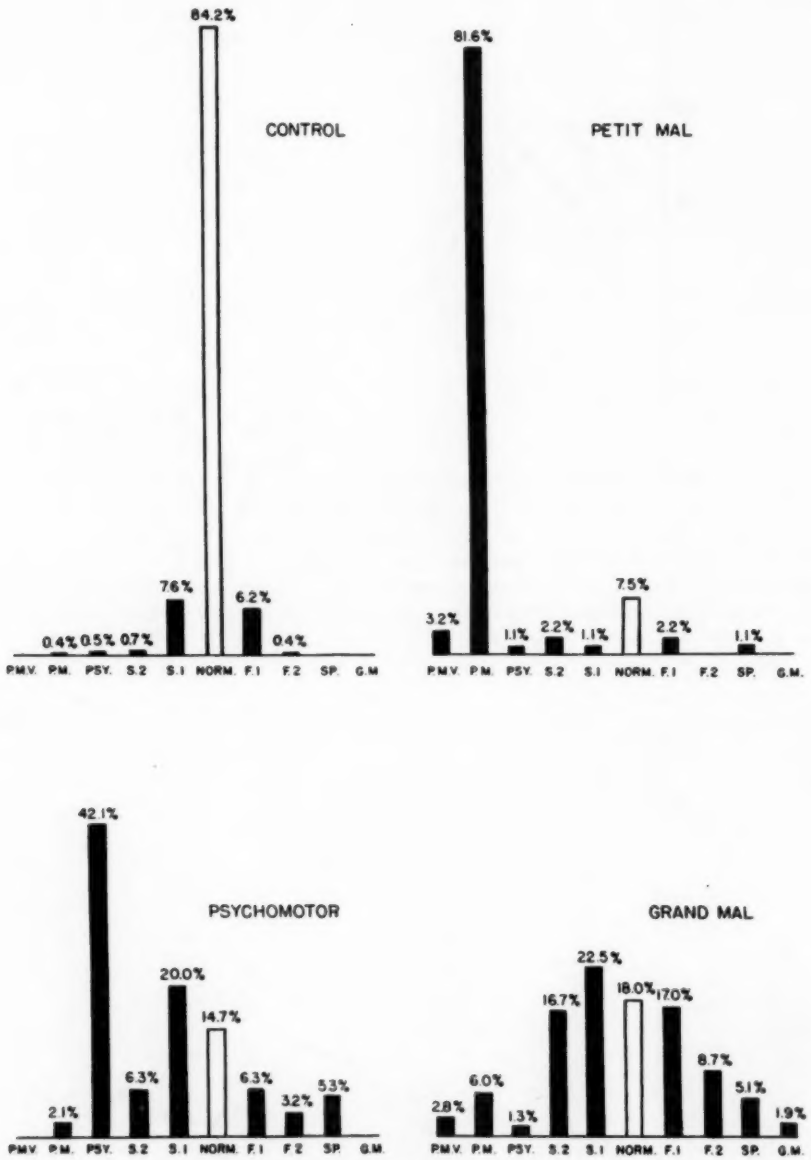

Fig. 7.—Percentage distribution of electroencephalographic types among 93 patients of all ages with a clinical diagnosis of petit mal only, 95 patients with the clinical diagnosis of psychomotor seizures only and 711 patients with the clinical diagnosis of grand mal seizures only, as compared with the percentage distribution for 1,000 adult controls. Categories are adjusted for age. The open columns indicate normal, and the black columns abnormal, electroencephalographic categories.

Figure 7 shows the distribution of electroencephalographic types for patients whose disorder was diagnosed as clinical petit mal only, clinical grand mal only or clinical psychomotor seizures only, and, for purposes of comparison, the dis-

tribution for the adult control group is given on an identical scale. For easier reference, a condensation of certain data in table 2 is given in table 3. Among patients with only one type of clinical seizure, the proportion of routine electroencephalograms that showed a type of seizure discharge corresponding to the type of clinical seizure reported in the patient's history was 81.6 per cent for petit mal (85 per cent when petit mal variants are included, see table 3), 42.1 per cent for psychomotor and 1.9 per cent for grand mal seizures. Table 3 also gives data on patients with more than one type of clinical seizure. From this table, it appears that a patient who has more than one form of clinical seizure is more likely to have a very abnormal record than one who has a single form of seizure, unless he has pure petit mal. The reasons for the high proportion of abnormal records in patients with petit mal and the close correspondence between the clinical and the electroencephalographic diagnosis of petit mal will be discussed later.

The preceding data are based on the recent random sample of 1,260 epileptic patients. Table 5 shows the incidence of clinical petit mal seizures and the 3 per second wave and spike formation of petit mal among the 10,488 persons whose electroencephalograms we have recorded in the past eight years. In this table, patients listed as having clinical petit mal seizures include those who had this

TABLE 5.—*Incidence of 3 per Second Wave and Spike Discharges in the Routine Electroencephalograms of Epileptic and Nonepileptic Patients*

Number of Patients	Clinical Group	Electroencephalographic Diagnosis (Three per Second Wave and Spike Pattern)	
		Number	Percentage
463	Epileptic patients with clinical petit mal	357	77.1
2,162	Epileptic patients without clinical petit mal	127	5.9
202	Relatives of epileptic patients	7	3.5
4,533	Nonepileptic neuropsychiatric patients	9	0.2
3,070	Normal controls	6	0.2

type of seizure either alone or in association with other types. The high degree of correlation between a history of clinical petit mal seizures and the presence of a 3 per second wave and spike pattern in the routine electroencephalogram is significant. The very low incidence of this pattern (1 : 500) among nonepileptic patients and normal controls is equally significant. As shown in table 5, 77 per cent of persons with a history of clinical petit mal seizures showed the 3 per second wave and spike pattern in their routine electroencephalograms. Because in some cases the petit mal type of discharge appears in the electroencephalogram only at rare intervals and may not be readily precipitated by overventilation, this percentage seeems reasonably high. Persons without a history of clinical petit mal seizures but with prolonged wave and spike discharges sometimes, on direct questioning, will report indefinite symptoms which could not be diagnosed as petit mal clinically but which, nevertheless, probably belong in that category.

COMMENT

When they were first described, the 3 per cent wave and spike discharge was identified with petit mal, and a crescendo burst of fast activity, with grand mal.[11] Later, a type of seizure discharge was observed which was believed to be char-

11. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

acteristic of psychomotor seizures.[12] Jasper and Kershman [13] questioned the propriety of naming a seizure discharge after the type of clinical seizure with which it appears. Arguments about nomenclature are so rarely profitable that the issue would not be raised were it not for the fact that recently Finley and Dynes [9] extended the criticism to include the terms and the correlations which led to their adoption. These authors reported that in their series of 369 epileptic patients only 13 per cent of the 68 persons with a clinical diagnosis of petit mal showed the characteristic petit mal type of seizure discharge in their routine electroencephalograms. They defined petit mal as a short seizure of almost any sort. Their data, therefore, demonstrate a lack of correlation between the type of electrical activity and the magnitude of the clinical seizure. As has been stated in a preceding paragraph, in our total series of 2,805 epileptic patients, 77 per cent of the 483 patients with a clinical diagnosis of petit mal, with or without some other type of seizure, showed the 3 per second wave and spike formation in their routine electroencephalograms; in the random sample of 1,260 cases, 73 per cent of the 293 patients with a clinical diagnosis of petit mal showed the characteristic wave and spike discharge. The essential specificity of the 3 per second wave

TABLE 6.—*Incidence of Certain Types of Electroencephalograms Among Epileptic and Nonepileptic Patients*

		Electroencephalographic Diagnosis				
			Nonparoxysmal			
No. of Patients	Clinical Group	Paroxysmal	Very Abnormal (S. 2 and F. 2)	Slightly Abnormal (S. 1 and F. 1)	Normal	Total
530	Epileptic patients under 20 years.....	51.3	16.6	23.6	8.5	100
730	Epileptic patients, 20 years and over...	29.2	22.0	32.4	16.3	100
202	Relatives of epileptic patients.....	5.9	4.0	37.1	53.0	100
418	Patients with organic neuropsychiatric disorders without epilepsy.....	1.2	43.3*	17.9	37.6	100
409	Patients with functional neuropsychiatric disorders without epilepsy.....	0.5	1.7	24.6	73.2	100
1,000	Normal adult controls.....	0.9	1.1	13.8	84.2	100

* Almost all show very slow (S. 2) activity.

and spike discharge for what in our series is clinically diagnosed as petit mal epilepsy is indicated in tables 2 and 5.

From table 6 it is apparent that seizure discharges in general are relatively specific for clinical epilepsy.[14] Among various groups, the proportions of records

12. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937.

13. Jasper, H. H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, Arch. Neurol. & Psychiat. **45**:903-943 (June) 1941. Jasper, H. H.: Electroencephalography, in Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, chap. 14, pp. 380-454.

14. This conclusion is at variance with an article published by us, entitled "The Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy" (Am. J. Psychiat. **95**:255-269 [Sept.] 1938). We believe that the conclusions of that paper were erroneous because the cases of "schizophrenia" on which it was based were too few and not typical instances of schizophrenia. Although the diagnosis of schizophrenia had been made, the fact that the patients had found their way into a neurologic clinic should have aroused suspicion. They showed certain clinical features that make it possible to distinguish them from the main group of schizophrenic patients. Their electroencephalograms resembled those of persons with psychomotor epilepsy, and, despite their schizoid behavior, they should probably be regarded as epileptic persons who were subject to more or less continuous psychomotor seizures. This problem will be given full consideration in a later report.

containing paroxysmal discharges were as follows: epileptic children, 51.3 per cent; epileptic adults, 29.2 per cent; epileptic patients of all ages, 38.5 per cent; relatives of epileptic patients, 5.9 per cent; persons with organic neuropsychiatric conditions, 1.2 per cent; persons with functional neuropsychiatric conditions, 0.5 per cent, and adult normal controls, 0.9 per cent. The group with organic disturbances, shown in table 6, represented the following conditions: cerebral trauma, 167 patients; tumor or abscess of the brain, 93 patients; vascular disease, 72 patients; syphilis of the central nervous system, 22 patients; parkinsonism, 10 patients; multiple sclerosis, 16 patients; encephalitis, 13 patients; choreoathetosis, 17 patients, and meningitis, 8 patients. Only patients who had no epileptic manifestations were included. Such a group is to some extent an arbitrary construct, for in the majority of these conditions convulsions are common. The incidence of very abnormal electroencephalograms tends to run parallel with the incidence of convulsions; for example, with tumor of the brain very abnormal records are common, and with parkinsonism they are rare. Therefore, it is the epileptogenicity, rather than the organicity, of these conditions that explains their high association with very abnormal electroencephalograms. The group with functional disorders was represented as follows: schizophrenia, 241 patients; manic-depressive psychoses, 46 patients, and migraine, 122 patients.

The routine electroencephalogram added confirmatory evidence to the clinical diagnosis of epilepsy in 38 per cent of the patients of all ages for whom clinical seizures have been observed; it added definite supporting evidence in an additional 20 per cent of such patients. However, in 13 per cent of clinically diagnosed epileptic patients the routine electroencephalogram was perfectly normal, and in 29 per cent it was not sufficiently abnormal to be indicative. Thus, in 42 per cent of the patients with clinically diagnosed epilepsy the routine electroencephalogram was of no great value. This fact must be recognized; it is an important limitation on the routine application of electroencephalography to the diagnosis of epilepsy. Any technic has its limitations, however, and the limitations of electroencephalography are, fortunately, not the same as those of clinical diagnosis; so the two technics can be used to supplement each other. In the detection of grand mal, for which clinical observation is adequate, routine electroencephalography is least valuable. In cases of petit mal, in which clinical manifestations are sometimes imperceptible, the electroencephalogram commonly shows a definite and characteristic abnormality. In cases of psychomotor epilepsy, the abnormal clinical behavior is often exceedingly complex, and the detection of a clearly defined seizure discharge of the psychomotor type may be of great diagnostic value.

In epilepsy, the more severe the clinical disorder, and the more frequent the seizures, regardless of their type, the greater the chance that some abnormality will appear in the routine electroencephalogram. Thus, it can be assumed that if a group of institutionalized epileptic subjects were classified according to our criteria, the percentage of abnormal electroencephalograms would be generally higher than in the present extramural group.

The amount and kind of anticonvulsant medication that is employed will modify the incidence of abnormal electroencephalograms in any large group of epileptic patients, but this is not as important a factor as might be supposed. Most of the patients in the present series were taking phenobarbital or phenytoin sodium. These drugs in ordinary doses do not produce abnormal waves in the electroencephalograms of normal persons, and although in epileptic patients the degree of abnormality may be changed, only rarely is it altered so much that the record

would be classified differently, and only very rarely does anticonvulsant medication abolish all abnormal activity.

If the electrical activity of the cortex is recorded during a seizure, the relation between the three main types of clinical seizures and the three types of seizure discharges is obvious. However, regardless of the occurrence or nonoccurrence of a clinically evident seizure, petit mal discharges are most commonly seen in association with a history of petit mal only; psychomotor discharges, in association with a history of psychomotor discharges only, and grand mal discharges, in association with a history of grand mal seizures only (fig. 7). Although typical grand mal patterns are rare in the routine electroencephalogram even of patients with clinical grand mal, when these patterns do occur, they are highly significant, and they are just as specific for clinical grand mal as the petit mal discharge is for clinical petit mal or the psychomotor discharge for clinical psychomotor seizures.

Several explanations can be advanced for the variation in the degree of correlation between different types of clinical seizures and the routine electroencephalograms. Of great importance is the fact that clinical petit mal seizures recur at shorter intervals than any other type. The average number of clinical seizures per year in patients with a given form of epilepsy is as follows: petit mal, 573 seizures; psychomotor, 217 seizures, and grand mal, 114 seizures.[10] The chances that a spontaneous clinical petit mal seizure will occur during the routine electroencephalographic examination are therefore five times as great as the chances that a spontaneous clinical grand mal seizure will occur. The relative chances of observing a paroxysmal discharge are still greater, for in any given period the number of subclinical seizure discharges (i. e., paroxysmal patterns unassociated with clinical manifestations) is several times greater than the number of clinical seizures.

Even if seizure discharges are fairly frequent, it is easy to see that none might appear during the twenty minute routine electroencephalographic examination. On the other hand, there is no time limit to the period of clinical observation; therefore, a clinical seizure, no matter how rare, is likely to be reported. This applies particularly to grand mal seizures. A similar explanation accounts for the consistent, though smaller, difference between the incidence of other types of clinical seizures and their characteristic seizure discharges.

Two additional factors are peculiarly favorable to the detection of the petit mal type of discharge in the routine electroencephalogram. First, the 3 per second wave and spike pattern is distinctive and is rarely confused with artefacts; consequently a single wave and spike formation, if typical, is perfectly reliable. Second, the wave and spike pattern of the petit mal type, with or without a clinical petit mal seizure, is much more readily precipitated by overventilation than any other type of seizure discharge, and, as part of the routine study, we have patients overventilate for two minutes.

The present concern with differences and similarities between various types of clinical seizures and seizure discharges may seem unwarranted. It is true that in many cases the patient has all three types of clinical seizures or a seizure of mixed type. Thus, it is obvious that the presence of one type of seizure does not exclude the presence of another. There is ample evidence, however, to indicate that the three types of clinical seizures are based on more or less separate neurophysiologic processes. They tend to appear and disappear at different ages (figs. 5 and 6), and they bear some relation to sex.[15] They are differently

15. Lennox, W. G., and Cobb, S.: Sex and Seizures, Tr. Am. Neurol. A. **67**:233-234, 1941.

affected by drugs [16] and by changes in body chemistry.[17] Different disturbances in acid-base equilibrium tend to occur with different types of clinical seizures.[18] Finally, and by no means the least significant, different types of clinical seizures are associated with different types of electrical activity.[1] The association has various aspects. A parallelism between the age incidence of clinically diagnosed petit mal seizures and the age incidence of petit mal seizure discharges has been shown (fig. 5), as has also a parallelism between the age incidence of clinically diagnosed psychomotor seizures and that of psychomotor seizure discharges (fig. 6). Correspondence between the therapeutic effect of drugs on the seizure discharge and on the clinical seizure (denied by Finley and Dynes) is a fact of great theoretic importance.[16b] Whether it can be put to practical use by the clinician is problematic; the end results of anticonvulsant therapy are at present approximately the same in cases in which electroencephalographic diagnosis has been made as in those in which it has not.[19] The close association between clinical petit mal seizures and wave and spike discharges when precipitated by overventilation [16b] or by lowering of the blood sugar [17a] is now so generally recognized that it needs no special emphasis.

SUMMARY AND CONCLUSIONS

The electroencephalograms of 1,000 adult control subjects and of 1,260 epileptic patients have been distributed on a scale of classifications based primarily on frequency. Each electroencephalogram is assigned to one of 18 categories, 9 of which are regarded as normal, 2 as slightly abnormal and 7 as very abnormal. The distribution for the control subjects forms a simple curve, with the mode at 10 per second. The distribution for a random sample of 730 adult epileptic patients is bimodal, with modes to the fast and the slow side of 10 per second.

No final and absolute value can be ascribed to the incidence of a given pattern in normal subjects, in epileptic patients or in subjects with other clinical classifications because the incidence of all types of normal and abnormal electroencephalograms varies with age and with the criteria used in diagnosis and classification. The greatest difference between the encephalograms of the normal subjects and those of the epileptic patients appears in the five electroencephalographic types classified as paroxysmal, i. e., those manifesting an abrupt and specific alteration of pattern. As compared with the records for the adult controls, the records of epileptic adults classed as paroxysmal are thirty-three times as numerous, those with very slow or very fast frequencies are twenty times as numerous and those with moderately slow or moderately fast frequencies are twice as numerous. Among children with epilepsy, the petit mal variant type of discharge occurs five times, the petit mal type two and one-half times and the grand mal type of discharge one and three-tenths times as commonly as among adult epileptic patients, whereas the psychomotor type of discharge and normal rhythms occur one-half and records with fast frequencies one-third as commonly.

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16. (*a*) Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in Treatment of Convulsive Seizures: Toxic Symptoms and Their Prevention, Arch. Neurol. & Psychiat. **42**:1053-1058 (Dec.) 1939; (*b*) Further Experiences with the Use of Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, Am. J. Psychiat. **96**:1023-1027, 1940. (*c*) Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electroencephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. **36**:1236-1245 (Dec.) 1936.

17. (*a*) Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Influence of the Blood Sugar Level on the Wave and Spike Formation in Petit Mal Epilepsy, Arch. Neurol. & Psychiat. **41**:1111-1116 (June) 1939. (*b*) Gibbs, Lennox and Gibbs.[2a]

18. Gibbs, Lennox and Gibbs.[2a] Nims and others.[2b]

19. Gibbs, F. A.: Diagnostic and Prognostic Value of the Electroencephalogram, J. A. M. A. **118**:216-219 (Jan. 17) 1942.

The electrical pattern during a seizure is distinctive for each of the three main types of seizures. When seizure discharges appear in the routine electroencephalogram, they tend to correspond to a type of clinical seizure already reported in that case. This correspondence is greatest for petit mal seizures, less evident for psychomotor seizures and least evident for grand mal seizures. It is important to recognize that we restrict the meaning of the term petit mal to a transient lapse of consciousness, with convulsive movements, if any, limited to a 3 per second clonic jerking of the eyelids, head or arms, a condition sometimes called pyknoepilepsy. The 3 per second wave and spike formation was found in 77 per cent of 463 patients with a history of petit mal, in 6 per cent of 2,162 epileptic patients without a history of petit mal, in 3.5 per cent of 202 relatives of epileptic patients and in only 0.2 per cent of 7,603 nonepileptic patients and normal controls.

Paroxysmal seizure discharges occur in the records of 38 per cent of epileptic patients of all ages; very slow or very fast frequencies, in the records of 20 per cent; moderately slow or moderately fast waves, in the records of 29 per cent, and normal rhythms, in the records of 13 per cent. Comparative data from epileptic patients, nonepileptic neuropsychiatric patients and controls indicate that a paroxysmal electroencephalogram, i. e., one manifesting seizure discharges, is strongly suggestive of epilepsy. Very slow or very fast nonparoxysmal waves in the electroencephalogram are suggestive of epilepsy or a related disorder. Moderately slow or moderately fast waves in the electroencephalogram are consistent with, but not definitely suggestive of, a diagnosis of epilepsy. In about 48 per cent of persons with a history of seizures, a routine electroencephalogram is of great value in diagnosis, and in about 42 per cent it is of little or no value.

818 Harrison Street.

ANTERIOR CHORDOTOMY

FURTHER OBSERVATIONS ON PHYSIOLOGIC RESULTS AND OPTIMUM MANNER OF PERFORMANCE

OLAN R. HYNDMAN, M.D.
AND
JULIUS WOLKIN, M.D.
IOWA CITY

Reports have been made on anterior chordotomy with reference to the location and disposition of the fibers of the spinothalamic tract [1]; anterior chordotomy as a cure for the pain and vomiting of gastric crises [2]; the influence of the anterior columns on hyperreflexia [3]; the effect of chordotomy on existing motor abnormalities,[4] and the effect of chordotomy on thermoregulatory sweating.[5]

PRESENT INVESTIGATION

The present report consists of an analysis of further studies, with particular reference to the physiology of the anterior and anterolateral columns and deductions concerning the location and manner of performance of chordotomy for optimum results.

The material is presented according to the following outline:

A. Influence on sensory system
   1. Tickle and itch
   2. Girdle pain
   3. Visceral pain—importance of splanchnic mediation
      Testicular pain and renal pelvic pain
      Effect of complete transverse lesion on testicular and renal pain

B. Influence on motor system
   1. Shivering
   2. Superficial and deep reflexes
   3. Reenforcement of deep reflexes

C. Influence on potency and sexual physiology

Read at the meeting of the Academy of Neurological Surgeons, Chicago, Oct. 3, 1942.

From the Department of Surgery, Neurosurgical Service, State University of Iowa College of Medicine.

1. Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract: A Clinical and Histologic Study, Arch. Surg. **38**:1036-1053 (June) 1939.

2. Hyndman, O. R., and Jarvis, F. J.: Gastric Crisis of Tabes Dorsalis: Treatment by Anterior Chordotomy in Eight Cases, Arch. Surg. **40**:997-1013 (May) 1940.

3. Hyndman, O. R.: Physiology of the Spinal Cord: I. Role of the Anterior Column in Hyperreflexia, Arch. Neurol. & Psychiat. **46**:695-703 (Oct.) 1941.

4. Hyndman, O. R.: Physiology of the Spinal Cord: II. The Influence of Chordotomy on Existing Motor Abnormalities, J. Nerv. & Ment. Dis., to be published.

5. Hyndman, O. R., and Wolkin, J.: Sweat Mechanism in Man: Study of Distribution of Sweat Fibers from the Sympathetic Ganglia, Spinal Roots, Spinal Cord and Common Carotid Artery, Arch. Neurol. & Psychiat. **45**:446-467 (March) 1941.

D. Influence on vascular system
Blood pressure; pulse; respiration; electrocardiogram; circulation time; venous pressure; carotid sinus reflex; renal function; results of cold pressor and glyceryl trinitrate (nitroglycerin) tests

E. Effect of section of Lissauer's tract

It has previously been stated [1] that after an uncomplicated section of the anterior and anterolateral columns on one or both sides there was no demonstrable loss of sensibility to touch, vibration or position, of stereognosis or of two point discrimination. Since that report it has been elected to do the chordotomies routinely at the level of the first dorsal segment (between the eighth cervical and the first dorsal root), and there has been no occasion to change the impression concerning these modalities, as determined by ordinary clinical tests.

In analgesic zones the patient can ordinarily distinguish hair pulling, but it is devoid of pain. If the foot is immersed in hot or cold water, the patient experiences nothing but touch sensation. Wetness is not perceived. (Temperature sense is probably indispensable to the recognition of wetness.) When the patient is placed in a heating cabinet or in a refrigerator, he states that he senses no change in the analgesic zones. The lower extremities always feel the same—comfortable, and usually slightly warm.

A. INFLUENCE OF ANTERIOR CHORDOTOMY ON VARIOUS TYPES OF SENSATION

TICKLE AND ITCH

By tickle is meant the sensation which is produced by lightly scratching the plantar surface of the foot and because of which the patient finds it difficult to hold the foot still in tests for the Babinski sign. Although it was previously stated that the sense of tickle was lost in 2 patients,[1] this sensation was neither abolished nor diminished in 125 patients with anterior chordotomy. It can be said with certainty that this particular sensation is not mediated through the anterior or the anterolateral column.

By itch is meant that disagreeable sensation which accompanies pruritus, scabies, "chigger" bites or the application of itch powder (from Mucuna pruriens), and for the relief of which it is difficult not to indulge in scratching. We have found the well known itch powder obtainable at novelty stores to be an excellent and effective means of testing for the sensation. Ten patients were tested. Three of these subjects had had unilateral and 7 bilateral chordotomy. In no instance was the itching sensation experienced in analgesic zones, although it was definite in normal zones. When the powder is rubbed on analgesic zones, such as the thighs, it produces an erythema and often causes the muscles to quiver and the extremities to jerk lightly. Evidently, the strong stimulus finds a reflex expression through the spinal cord, but the patients strictly deny having any subjective sensation whatever. Except for the remote possibility of mediation through the anterior column, which is unlikely, it can be said with certainty that the sensation of itch is mediated through the spinothalamic tract and is therefore a form of the modality of pain or temperature or both. It most likely involves only the pain sense. As a result of these studies, we feel it can be predicted with confidence that the itching of pruritus would be abolished by anterior chordotomy.[6]

6. We have applied the itch powder to anhidrotic zones after sympathetic ganglionectomy in a number of patients. Sympathectomy did not diminish or have any influence on the sensation of itching.

Comment.—It is not surprising that the sense of tickle remains unaltered after section of the spinothalamic tracts. It is associated with the sense of touch and is modified greatly by the "frame of mind." Most persons are ticklish over the ribs or in the axilla. Feathers drawn across the lips become unbearable, and cotton softly brushed on the skin, particularly on the hairy parts, causes tickling. If children are approached without suggestion, their ribs and axillas may be palpated without undue reaction, but if tickling is suggested it is a different matter. Tickle is associated with laughter, hence the expression, "You tickle me."

It is equally not surprising that itch is a modified form of pain and is abolished by section of the spinothalamic tract. The sensation is unpleasant and is in no way modified by a "frame of mind." The agents that are productive of itch must at least penetrate the corneum of the skin. For a sharp instrument, such as a pin, to initiate the sense of pain the point must penetrate into the corneum, and possibly through it. This fact indicates that the endings of pain fibers must actually be touched to be stimulated, whereas transmitted pressure is adequate to stimulate the endings of touch fibers. The thin corneum is evidently, and fortunately, sufficient to blanket the pain endings from the usual touch and pressure stimuli. If the corneum is shaved off, light touch stimuli will provoke pain. The only possible difference between the head and the point of a pin is that the latter penetrates the corneum.[7] The itch powder (Mucuna pruriens) consists of tiny, sharp barbs of hairlike needles, which when rubbed on the skin penetrate the corneum. Each acts as a light painful stimulus, and the total effect of hundreds of these causes itching. The barbs probably contain a formicating substance, which enhances the stimulation, and the part to which they are applied often becomes erythematous.

GIRDLE PAIN

About half the patients on whom anterior chordotomy is performed experience girdle pain of varying degree. If such pain develops, it is likely to last indefinitely, although it usually grows less severe with time. It has appeared to be rather anoying to some patients. The pain is constant and of a burning, aching character, similar to that associated with peripheral neuritis. It is usually localized to a narrow band, which represents the level of transition from algesia to analgesia. That is, the girdle pain corresponds not to the segment at which the chordotomy was done but to the level of sensory change on the skin. We formerly thought that such pain might be due to injury to sensory roots when the chordotomy was performed, but the fact just stated opposes such an explanation. The zone to which the pain is referred is usually hyperesthetic to brushing and pinching and tender to deep pressure. At present we feel that the girdle pain is in some way due to a physiologic disturbance in sensation in which sensibility to pain shades off into insensibility to pain. The same type of pain has in some patients followed section of posterior roots. Since the pain is of the same character as that which follows chordotomy, we believe the pathophysiologic mechanism is the same in the two cases. This type of pain is to be

7. During every moment of the conscious state, touch and pressure sensations are perceived. Sensations of pain are not provoked unless the external stimuli are of an injurious character. Wilson and Mussey (Proc. Staff Meet., Mayo Clin. **17**:11-16 [Jan. 7] 1942) account for this fortunate arrangement as follows: "As far as the somatic sensory apparatus is concerned, it is obvious that under ordinary circumstances it is unlikely that the end-organs of the discriminative senses (touch, temperature, and so forth) could be stimulated without at the same time having the pain receptors also stimulated. Yet the sensations of the discriminative senses reach the level of consciousness and those of pain may not because of being inhibited in the posterior horns of the spinal cord." It seems to us that the mechanism under consideration is contingent on the character of the end organs and on the stimulus that is adequate for each.

distinguished from strictly referred, or "fantom," pain, which is felt in a part that is not present or in a part that is anesthetic.

The incidence of girdle pain was less frequent when the chordotomy was performed at the first dorsal segment than it formerly was, when the chordotomies were routinely made at the second or third dorsal segment. This led us to suspect that the sympathetic fibers might in some way be implicated. Consequently, in the patient described in case 2 we removed the inferior cervical and the first dorsal ganglion on the right side. This did not relieve the pain; on the other hand, the ganglionectomy did not render the zone of the girdle pain anhidrotic. At the time we were thinking in terms of afferent sympathetic fibers which might enter the cord at a high level. We have since come to the conclusion that if sympathectomy is to be effective in relieving certain types of extravisceral pain, the efferent sympathetic fibers which supply the painful part must be completely severed. Hence the sympathectomy in this case may have been entirely inadequate for the purpose. In case 1 (L. W.) the sympathectomy can be considered adequate; nevertheless, it had no influence on the pain.

CASE 1.—L. W., a white woman aged 48, was admitted to the hospital on April 17, 1939. She had moderately advanced essential hypertension and complained of severe headache.

On April 26 an anterior chordotomy was done between the first and the second dorsal root on both sides, and the upper four posterior dorsal roots were sectioned on both sides. The patient had suffered from migraine-like headaches all her life. The operation was designed to obtain the good effect of anterior chordotomy on hypertension[8] and to interrupt all possible afferent sympathetic pain fibers that might enter the central nervous system below the first dorsal segment. It was felt that this would include fibers from the vessels of the head. This patient was one of a few in whom the reduction in blood pressure persisted. Before operation the average blood pressure was 200 systolic and 120 diastolic. Twenty months later the pressure was 110 systolic and 80 diastolic. She stated that her headaches were only about one-fourth as bad as they formerly were.

After the operation, however, she complained of persistent hyperesthesia and girdle pain in the upper part of the chest and down the inner aspects of the arms—that is, at the upper margin of cutaneous analgesia. Nine months after the operation this girdle pain was so annoying that an attempt was made to relieve it. Procaine hydrochloride was injected into the lumbar subarachnoid space and the patient's head gradually lowered. The level of developing anesthesia was followed, and when the distribution of the eighth cervical nerves became involved the patient stated that the pain and hyperesthesia disappeared. Later an injection of procaine into the region of each stellate ganglion appeared to give some relief, and on the strength of this test a cervicodorsal ganglionectomy was carried out on both sides. The inferior cervical and the first dorsal ganglion were removed on the left side, and the inferior cervical and the upper two dorsal ganglia, on the right side. After this procedure the patient felt that she had less restricted movement of the upper extremities, but the pain was not relieved.

CASE 2.—L. C., a white woman aged 35, was admitted because of essential hypertension.

On March 13, 1939 a modified chordotomy was done on both sides, as shown in figure 1. The sections were made at the second dorsal segment. In addition, the anterior and posterior roots from the first to the fifth dorsal segment inclusive were cut on both sides. In addition to the sensory losses in the distribution of the first to the fifth dorsal spinal nerve, there was an area of analgesia reaching to just above the knee on each side, a result in keeping with the principles given in a previous report[1] concerning the distribution of fibers in the spinothalamic tract.

(This case is discussed further in the sections on "Visceral Pain" and "Potency and Sexual Physiology.")

After the chordotomy and the rhizotomy a persistent girdle pain developed on the right side in the distribution of the sixth and seventh dorsal nerves, that is, at the lower margin of the area of analgesia due to the rhizotomy. This zone was hyperesthetic, tender to pressure and constantly painful. The patient returned to the hospital on several occasions with this as her only complaint. Ten months after the operation, procaine was injected into the lumbar subarachnoid space and the level of anesthesia followed as it crept upward.

8. Hyndman, O. R.; Wolkin, J., and Paul, W. D.: Effect of Anterior Chordotomy on Essential Hypertension, Proc. Soc. Exper. Biol. & Med. **44**:304-306 (May) 1940.

When this level of anesthesia merged with that due to the rhizotomy, all pain and tenderness disappeared. Later procaine injected into the region of the right stellate ganglion appeared to be beneficial, and for this reason the inferior cervical and the first dorsal ganglion on the right side were removed, on Feb. 8, 1940. The procedure had no influence on the pain.

On Oct. 31, 1941 a routine anterior chordotomy was done on the left side between the eighth cervical and the first dorsal root. This was followed by complete analgesia on the right side up to and including the area of analgesia due to the previous rhizotomy. All pain and tenderness were abolished.

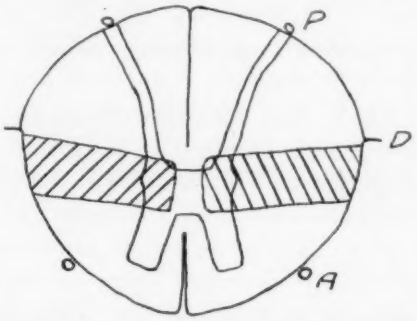

Fig. 1.—Diagrammatic representation of a modified chordotomy which was intended to sever sympathetic tracts in the cord, in an effort to treat essential hypertension. *A* indicates anterior root filaments; *D*, the dentate ligament, and P, posterior root filaments.

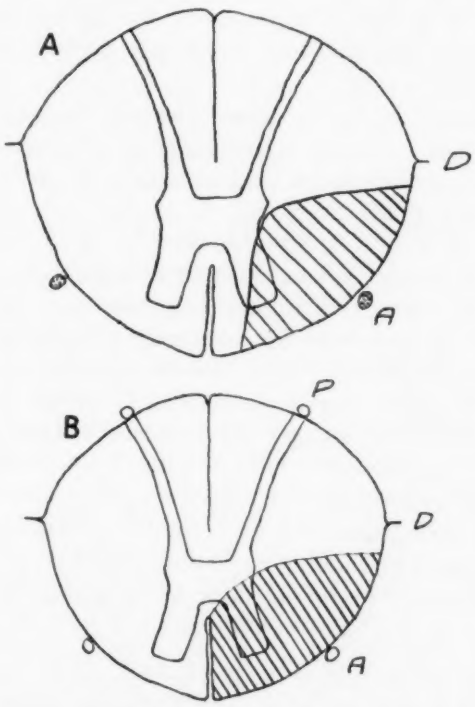

Fig. 2.—Diagrammatic representation of the manner in which a routine anterior chordotomy is done to relieve pain. While it is felt that the section shown in *A* would be sufficient, most of our sections have approached more closely that shown in *B*.

Case 3.—M. C., a white man aged 69, was admitted because of gastric crises of tabes dorsalis.

On Oct. 30, 1941 anterior chordotomy was done at the first dorsal segment. The regular complete section was made on the right side as shown in figure 2, and hence analgesia

was complete on the left side to the line of the nipple. On the left side the section was begun about halfway between the dentate ligament and the line of the anterior roots. Pain sensibility up to about the midthigh on the right side was about 60 per cent of normal, and from there up to the nipple line there was complete analgesia. This result is in keeping with the principles given in a previous report.[1]

The patient complained of pain, tenderness and hyperesthesia from the midthigh down. The pain was similar in every respect to girdle pain and was still present at a follow-up examination two months later. The gastric crises were completely abolished.

(This case is discussed in the section on "Visceral Pain.")

In an analysis of the peculiar type of pain under discussion certain characteristics stand in relief.

1. The pain is never localized to a completely analgesic or anesthetic zone. In our experience it has never been localized to a normally innervated zone. It is localized to a zone where pain sensibility is present, but deficient.

2. The pain may follow rhizotomy or chordotomy, and it is not unlikely that the pain and hyperesthesia which sometimes follow lesions of peripheral nerves may be of the same cause and nature. The pain does not always follow rhizotomy and chordotomy, and after bilateral operation it may occur on only one side.

3. The locus of the pain appears to be peripheral, and the most striking common factor is a partial, but not complete, elimination of pain fibers to the part. Case 3 is a striking example in point.

4. On the basis of a limited experience, we do not believe that the sympathetic fibers play any significant role, inasmuch as sympathectomy has failed to give relief.

5. If a spinal anesthetic is administered, the pain disappears as soon as the part involved becomes analgesic. Also, chordotomy at a higher level which is followed by analgesia in the formerly painful zone abolishes the pain.

VISCERAL PAIN

We have been interested in evaluating the effect of chordotomy on visceral pain. It is not necessary at this time to consider the various theories of reflex pain. There is abundant evidence that pain may be initiated in visceral structures if given an adequate stimulus. White and Smithwick [9] gave an account of this subject and compiled a table to show (as well as is known at present) the segments of the cord into which lead sensory fibers from various viscera. Bentley and Smithwick [10] found that epigastric pain produced by insufflation of a balloon in the duodenum was abolished by bilateral section of the splanchnic nerves and removal of the lower thoracic and first lumbar dorsal ganglia. Adson [11] and Leriche [12] produced pain by stimulation of the splanchnic nerves, and Learmonth [13] caused pain to be referred to the bladder by crushing the superior hypogastric plexus.

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9. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System: Anatomy, Physiology, and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

10. Bentley, F. H., and Smithwick, R. H.: Visceral Pain Produced by Balloon: Distension of the Jejunum, Lancet **2**:389-391 (Sept. 28) 1940.

11. Adson, A. W.: Splanchnic Pain, Proc. Staff Meet., Mayo Clin. **10**:623-624 (Sept. 25) 1935.

12. Leriche, R.: Des douleurs provoqués par l'excitation du bout central des grands splanchniques (douleurs cardiaques, douleurs pulmonaires) au cours des splanchnicotomies, Presse méd. **45**:971-972 (June 30) 1937.

13. Learmonth, J. R.: Neurosurgery in the Treatment of Diseases of the Urinary Bladder: II. Treatment of Vesical Pain, J. Urol. **26**:13-24 (July) 1931.

The importance of this information in relation to chordotomy is that visceral innervation does not correlate topographically with somatic dermatomes. After chordotomy one tests for a cutaneous level below which there is analgesia. The test is ordinarily made by means of the simple pinprick. The results obtained apply only to the skin, but are probably a fair index to somatic analgesia in the deeper tissues as well. However, if there is analgesia up to the cutaneous level of the sixth dorsal dermatome, it does not necessarily follow that abdominal viscera below that level will be insensitive to pain. This is particularly true in respect to pain mediated by the splanchnic nerves. In short, one must give regard to the viscerosensory pathways to the cord rather than to visceral topography.[14]

Chordotomy is most frequently indicated to relieve intractable pain that is probably composed of both visceral and somatic elements—hence the importance of taking into consideration all the possible pathways for pain. After chordotomy was introduced and established on a sound physiologic basis,[15] there followed an era in which the procedure lost or failed to maintain high respect. Results were confusing, inconstant and unpredictable, and pain was not as completely relieved as it should have been. We now feel that these inadequate results were due not to inconstancies in the anatomy and physiology of the pain tracts but to the fact that incisions were not made deep enough into the cord, were not carried sufficiently far anteriorly and mesially and were not made consistently high enough in the cord. If these requirements are fulfilled, the results of chordotomy will be adequate and predictable.

It has been proposed[16] that ascending visceral pathways run upward within the spinal cord by short fibers, with many relays and synapses, which have a juxtagriseal position. White and Smithwick[9] stated that it is likely that pain from distention of hollow viscera ascends, at least in part, in the posterior columns. This has not been our impression. From our results we have not been able to conclude otherwise than that the spinothalamic bundle of fibers is the physiologic unit through which is mediated the modality of pain of whatever source, and that if this bundle is completely severed, pain can no longer be initiated in the region of its distribution. The region of distribution deserves further consideration, however, and no doubt if only a few fibers remain intact they could account for considerable pain. It is in respect to these matters that we have studied the influence of chordotomy on visceral pain. Two indicators were studied—the testis and the renal pelvis. Dr. Rubin H. Flocks, of the department of urology, performed the urologic studies.

Testicular Pain Sense.—A severe aching and nauseating pain is provoked when the normal testis is squeezed. The pain, in addition to being felt locally, is often referred to the abdomen. The nerve supply to the testis consists of the spermatic plexus from the sympathetic nerves, joined by filaments from the pelvic plexus which accompany the artery of the ductus deferens.[17]

14. If the afferent pain-bearing fibers in the walls of vessels of the extremities are comparable to viscerosensory fibers, the same reasoning may apply. If the skin of, say, a lower extremity is analgesic from the level of the twelfth dorsal dermatome down, does it follow that the deeper tissues and vessels are analgesic to the same degree? The answer awaits more rigorous clinical tests or more knowledge concerning the pathways of vascular pain fibers.

15. Spiller, W. G., and Martin, E.: The Treatment of Persistent Pain of Organic Origin in the Lower Part of the Body by Division of the Anterolateral Column of the Spinal Cord, J. A. M. A. **58**:1489-1490 (May 18) 1912. Frazier, C. H., and Spiller, W. G.: Section of the Anterolateral Columns of the Spinal Cord (Chordotomy), Arch. Neurol. & Psychiat. **9**:1-21 (Jan.) 1923.

16. White and Smithwick,[9] p. 142.

17. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 20, Philadelphia, Lea & Febiger, 1918.

The particular type of severe pain produced by squeezing a testis is undoubtedly mediated entirely by sympathetic nerves, that is, viscerosensory nerves. In our own subjects we have demonstrated the following facts: 1. Complete lesion of the conus medullaris, with elimination of the function of all the sacral nerves, did not diminish testicular pain sense. 2. A complete transverse lesion of the cord at the middorsal level completely abolished testicular sensibility to pain. Two patients were studied after a complete transverse lesion, with a sensory level at the eleventh dorsal segment (1 inch [2.54 cm.] below the umbilicus). One patient retained only a trace of pain sense in the right testis. The other patient retained about 30 per cent of normal sensibility to pain in the left testicle, but the right was painless (see section on "Complete Transverse Lesions").

The following 9 patients were carefully studied after anterior chordotomy. Five patients had bilateral and 4 patients unilateral chordotomy. The testicles were tested for pain sense on numerous occasions. They were not recorded as painless unless they were absolutely so on being severely squeezed. In every case the testicles were painful to pressure before chordotomy.

CASE 4.—E. J., a man aged 58, had recurrent carcinoma of the rectum. Anterior chordotomy was performed bilaterally at the first dorsal segment. The level of analgesia reached the cutaneous level of the fourth dorsal segment on each side. Both testicles were insensitive to pain on being squeezed.

CASE 5.—R. A., a man aged 27, had a chondrosarcoma of the lumbar portion of the spine. Anterior chordotomy was done bilaterally at the first dorsal segment. Analgesia was complete below the level of the eighth dorsal segment on both sides. Both testicles were painless on being squeezed.

CASE 3.—M. C., a man aged 69, had gastric crises of tabes dorsalis. Anterior chordotomy was performed bilaterally at the first dorsal segment. Analgesia was complete below the fifth dorsal segment on both sides except on the right lower extremity from the region of the midthigh down (see section on "Girdle Pain"). In this zone analgesia was about 60 per cent of normal. Squeezing of the right testicle caused very slight pain; the left testicle was insensitive to pain.

CASE 6.—H. T., a man aged 35, had gastric crises of tabes dorsalis. Anterior chordotomy was done bilaterally at the first dorsal segment. Nine months later analgesia was found to be complete below the level of the xiphoid process. Both testicles were painless on being squeezed.

(This patient is discussed further in the section on "Potency and Sexual Physiology.")

CASE 7.—A. R., a white man, was admitted because of gastric crises of tabes dorsalis. Anterior chordotomy was done on Feb. 8, 1939 at the second dorsal segment on both sides, and analgesia reached the level of the sixth dorsal dermatome. Both testicles were painless on being squeezed.

(This patient is discussed further in the section on "Potency and Sexual Physiology.")

CASE 8.—N. W., a white man aged 44, was admitted with an inoperable carcinoma of the rectum. He complained of severe and constant pain in the distribution of the right sciatic nerve only. Anterior chordotomy at the first dorsal segment on the left side (Aug. 10, 1942) resulted in analgesia to the fifth dorsal dermatome on the right side.

The right testicle was about 20 per cent as sensitive to squeezing as was the normal left testicle.

CASE 9.—J. M., a man aged 71, had a recurrent hypernephroma on the right side. Anterior chordotomy was done at the first dorsal segment on the left side. Analgesia was complete below the fifth dorsal dermatome on the right side. The left testicle was normally painful to pressure. The right testicle was about half as painful as the left, but was not completely painless.

CASE 10.—R. S., a man aged 53, had recurrent carcinoma of the bladder, with pain on the left side only. Anterior chordotomy was performed at the first dorsal segment on the right side. Analgesia was complete below the fifth dorsal dermatome on the left side. The right testicle was normally painful on pressure, but the left was insensitive to pain.

(This case is discussed further in the section on the "Motor System.")

CASE 11.—F. B., a man aged 76, had postherpetic neuralgia in the distribution of the second to the fourth dorsal nerves inclusive on the left side. Anterior chordotomy at the first dorsal segment on the right side was supplemented by section of the posterior root of the first dorsal nerve on the left side and by section of Lissauer's tract at the same level on the left side. Analgesia was complete to and including the first dorsal dermatome on the left side.

There was only a slight trace of pain when the left testicle was squeezed. The right testicle was normally painful. On the day following operation the patient's bladder became distended and was the source of considerable pain. He stated that there seemed to be a sharp dividing line in the midsagittal plane, and he felt bladder pain only on the right side of this plane.

Summary and Conclusion: In all but 1 of the 5 patients who had bilateral chordotomy both testicles were painless. This patient retained about 60 per cent algesia from the midthigh down on the right side, for reasons given in the section on "girdle pain." His right testicle was almost, but not completely, painless on being squeezed.

Of the 4 patients who had unilateral chordotomy, 1 had insensitivity to pain in the testicle on the analgesic side; 1 had 50 per cent reduction in sensitivity, 1 had 80 per cent reduction and 1 had only a slight trace of pain sense.

Therefore, it may be said that bilateral anterior chordotomy abolishes testicular sensitivity to pain, a result indicating that this type of visceral pain is mediated through the spinothalamic tracts. Unilateral chordotomy may only partially abolish testicular pain, an indication of a variable bilateral representation.

Pain in the Renal Pelvis.—Malisoff, Light and Macht [18] stated that afferent fibers supplying the kidney are mainly components of the tenth, eleventh and twelfth thoracic nerves. Renner [19] described sensory endings in the musculature of the renal pelvis, in the renal capsule and in the adventitia and media of renal vessels. He stated that only a few myelinated fibers are present in the parenchyma, but they occur in greater abundance in the region of the renal calices and pelvis. According to Müller,[20] pain seems to be a specific property of the renal pelvis.

Gubergritz and Itschenko [21] showed that ureteral catheterization gave rise to no pain in animals but that distention of the renal pelvis with water did. The pain was abolished by section of nerves along the renal vessels. They concluded that pain sense was transmitted along the renal plexus and into the cord by way of the sympathetic chain (splanchnic nerves).

While we were performing studies on the kidney in the following cases, we had an opportunity to test for the presence or absence of pain in the renal pelvis after chordotomy.

CASE 12.—C. J., a white woman aged 51, had gastric crises of tabes.

On Nov. 5, 1941 bilateral anterior chordotomy was done at the first dorsal segment. A level of analgesia was found at the fifth dorsal dermatome. The gastric crises were abolished.

Urologic Study (November 19).—The capacity of the bladder was somewhat diminished; the force was normal; no residual urine was noted. A no. 60 T ureteral catheter was passed on each side. The capacity of the right renal pelvis was 12 cc. and that of the left 16 cc. The patient could not discriminate between hot and cold water in the renal pelves and did not sense pain on forceful distention.

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18. Malisoff, S. S.; Light, I. R., and Macht, M. B.: Asymptomatic Renal Destruction, with a Discussion of the Neurophysiology of Pain Production in the Kidney, J. Urol. **46**:209-215 (Aug.) 1941.

19. Renner, O., cited by Müller,[20] pp. 287-295.

20. Müller, L. R.: Die Lebensnerven, Berlin, Julius Springer, 1924.

21. Gubergritz, M. M., and Itschenko, I. N.: Zur Frage der Entstehung der Schmerzempfindung in den Nieren, Ztschr. f. d. ges. exper. Med. **52**:619-633, 1926.

CASE 13.—N. B., a white woman aged 41, had gastric crises of tabes.

On July 6, 1940 bilateral anterior chordotomy was done at the second dorsal segment. The level of cutaneous analgesia was slightly below the fifth dorsal dermatome. The result was good, however, and the patient was completely relieved of crises for nine months. She then returned, complaining of a recurrence of abdominal pain, tenderness and vomiting. The signs and symptoms were not typical of gastric crises, but were undoubtedly related to the former crises. The abdominal pain was almost continuous. The abdomen was soft and tender to palpation even below the umbilicus.

The level of cutaneous analgesia had dropped to a little below the seventh dorsal dermatome.

Urologic Study (Oct. 8, 1941).—The bladder force was small and the capacity great. A no. 60 T ureteral catheter was passed on each side. There was no residual urine in the renal pelves. The right pelvis had a capacity of 33 cc. and the left a capacity of 38 cc. On forceful distention of either pelvis the patient experienced a severe "bursting" pain, localized to the region of the umbilicus. The pain was not localized, as is normally the case, at the costovertebral angles. She could not distinguish between hot and cold water in either pelvis.

Operation (October 17).—The anterior chordotomy was repeated. The section on the right side was made between the fifth and the sixth cervical root, and that on the left side, between the sixth and the seventh cervical root. After this procedure the cutaneous analgesia reached the eighth cervical level on the left and the first dorsal level on the right. The abdominal pain and tenderness were abolished.

Urologic Study (November 15).—The same test was carried out as on October 8. When the renal pelves were distended, the patient had a sensation of fulness, which she referred to the proper side, but pain was not felt.

CASE 2.—L. C. had a modified chordotomy on both sides on March 13, 1939, in addition to section of the anterior and posterior roots from the first to the fifth dorsal segments inclusive. There resulted a level of analgesia up to a little above the knees and the sensory loss that is normal after section of the posterior roots. This case is discussed in greater detail under "Girdle Pain."

On Oct. 31, 1941 complete anterior chordotomy was done on the left side between the eighth cervical and the first dorsal root. This was followed by complete analgesia on the right side up to and including the area of analgesia due to the previous rhizotomy.

Urologic Study.—On November 15 the force and capacity of the bladder were found to be normal, and there was no residual urine. No. 60 T ureteral catheters were passed. The capacity of the right pelvis was 10 cc., and that of the left was 12 cc. On forceful distention of the right pelvis only slight pain was felt. On distention of the left pelvis the pain was normally severe.

Summary and Conclusion: In patient 12 a bilateral anterior chordotomy at the first dorsal segment, followed by analgesia to the fifth dorsal dermatome, completely abolished pain in the renal pelvis.

In patient 13, after bilateral chordotomy at the second dorsal segment, the level of analgesia was for a time at the fifth dorsal segment, and after about nine months it dropped to a little below the seventh dorsal segment. This was accompanied by a recurrence of abdominal pain and tenderness. At this time forceful distention of the renal pelves caused severe pain, with atypical localization. The chordotomy was repeated at a low cervical level, and the level of analgesia was brought to the eighth cervical dermatome on the left side and to the first dorsal dermatome on the right. The abdominal pain and tenderness and the pain in the renal pelvis were abolished.

In patient 2 a modified bilateral chordotomy resulted in cutaneous analgesia to a little above the knees. Later a complete anterior chordotomy on the left side only at the first dorsal segment resulted in a high level of analgesia on the right side. There were slight pain in the renal pelvis on the right side and normal pain on the left side.

Although this group of patients is small, one may tentatively conclude that a bilateral chordotomy which results in cutaneous analgesia as high as the fifth dorsal

dermatome will eliminate pain in the renal pelvis due to forceful distention. If cutaneous analgesia reaches only to the seventh dorsal level, the pain in the renal pelvis is not completely eliminated.

A unilateral anterior chordotomy resulting in complete analgesia to the first dorsal dermatome on the opposite side will largely, but may not completely, abolish pain in the renal pelvis on the analgesic side. Hence the renal pelvis is comparable to the testis in having a partial bilateral representation.

For purposes of comparison, we have made studies on the sensibility of the testis, bladder and renal pelvis in a number of patients with complete transverse lesions of the cord at various levels.

Complete Transverse Lesions of the Cord and Cauda Equina.—Third Lumbar Segment.

D. F., a man aged 22, had a fracture at the first lumbar segment two years before. There was a complete transverse lesion of the cauda, with a sensory level at the third lumbar dermatome.

Urologic Study (Oct. 9, 1942): Bladder. Sensibility to heat, cold and pinching was absent. The residual urine measured 40 cc.; the capacity of the bladder was 350 cc. Uninhibited contractions occurred with filling at 50 cc. The internal sphincter and the bladder were spastic. The trigone and the bladder wall were hypertrophic.

Renal pelves. The capacity of the right renal pelvis was 30 cc., and that of the left was 28 cc. Pain sense was normal when the pelves were distended.

Note: The patient has learned to evacuate the bowel and bladder by external abdominal pressure. He has no sensation of fulness in or sense on evacuation of either the bowel or the bladder.

Testicles. Normal pain was experienced when the testicles were squeezed.

Twelfth Dorsal Segment.

E. A., a white woman aged 38, had a fracture of the eleventh dorsal vertebra on June 26, 1941. There was a complete transverse lesion, with a sensory level at the twelfth dorsal dermatome.

Urologic Study (Dec. 3, 1942): Bladder. Sensibility to heat, cold and pinching was absent.

Renal pelves. The capacity of the right pelvis was 14 cc., and that of the left was 10 cc. Distention was not associated with pain on the right side, but there was definite pain on the left. Pain was referred normally and was apparently of the usual severity.

Eleventh Dorsal Segment.

E. M., a white youth aged 19, had a fracture of the twelfth dorsal vertebra on May 16, 1942. There was a complete transverse lesion with sensory level at the eleventh dorsal dermatome.

Urologic Study (Oct. 9, 1942): Bladder. Sensibility to heat, cold and pinching was absent.

Renal pelves. The capacity of the right pelvis was 30 cc., and that of the left was 35 cc. There was no pain when the right pelvis was distended. A mild, vague pain, not typical of renal pain, was referred to the lower portion of the abdomen when the left pelvis was distended.

Testicles. The right testicle was painless on being squeezed. Sensitivity to pain of the left testis was about 30 per cent of normal.

R. R., a white man aged 49, had a fracture of the eleventh dorsal vertebra on June 14, 1942. The sensory level was at the eleventh dorsal dermatome.

Urologic Study (Nov. 27, 1942): Bladder. Sensibility to heat, cold and pinching was absent.

Renal pelves. The capacity was 5 cc. on each side. Distention failed to cause pain on either side.

Testicles. The left testicle was insensitive to pain on being squeezed. When the right testicle was squeezed hard, mild pain was referred to the upper portion of the abdomen.

Tenth Dorsal Segment.

D. H., a white woman aged 20, had a compression fracture of the tenth and eleventh dorsal vertebrae in 1937. There was a complete transverse lesion, with the sensory level at the tenth dorsal dermatome.

Urologic Study (Oct. 9, 1942): Bladder. Sensibility to heat, cold and pinching was absent.

Renal pelves. The capacity of the right pelvis was 4 cc., and that of the left was 6 cc. Distention caused no pain on either side.

Sixth Dorsal Segment.

H. R., a white man aged 26, had a compression fracture of the fifth and sixth dorsal vertebrae twenty days before. There was a complete transverse lesion, with a sensory level at the sixth dorsal dermatome.

Urologic Study (Feb. 16, 1942): Bladder. The wall was flaccid; sensibility to heat, cold and pinching was absent.

Renal pelves. The capacity was 30 cc. on each side. Distention caused no pain.

Testicles. There was complete insensitivity to pain on both sides.

Comment: A complete lesion at the third lumbar segment did not influence sensitivity to pain in the testis or renal pelvis. A complete lesion at the sixth dorsal segment and one at the tenth dorsal level completely abolished pain sense in the renal pelves. A lesion at the twelfth dorsal level abolished renal pain on one side. A lesion at the eleventh dorsal level abolished renal pain on both sides in 1 case and on one side and almost so on the other in another case. These results indicate that visceral sensation from the renal pelvis enters the cord at the eleventh and twelfth dorsal levels. It appears that the pathway mediating testicular pain sensation closely parallels that for renal pain sensation.

B. INFLUENCE OF ANTERIOR CHORDOTOMY ON THE MOTOR SYSTEM

SHIVERING

Three patients were exposed in a refrigerator in which the temperature was from 0 to 5 C. The patients were nude except for a loin cloth, and they remained in the refrigerator until shivering was well advanced.

CASE 14.—L. K., a white man aged 59, had gastric crises of tabes dorsalis. Anterior chordotomy was done on Nov. 13, 1939 between the fifth and sixth cervical segments on the left side and between the sixth and seventh cervical segments on the right side. There was a level of analgesia at the first dorsal dermatome on both sides.

When the subject was in the refrigerator, there was vigorous shivering of the shoulders and upper extremities, but none below.

CASE 10.—R. S., a white man aged 53, was admitted because of severe pain in the left sacroiliac region and the left lower extremity, due to metastases from a carcinoma of the bladder.

On Sept. 8, 1941 anterior chordotomy was done on the right side at the first dorsal segment. The level of cutaneous analgesia reached the fifth dorsal dermatome on the left side.

On September 21 the patient was placed in the refrigerator for twenty-five minutes. There was vigorous shivering of both shoulders and of the muscles of the back, loin and thigh on the left side. There was no shivering below the scapula on the right.

CASE 15.—On Dec. 20, 1939 A. S. had a bilateral anterior chordotomy at the seventh cervical segment on the left side and at the eighth cervical segment on the right side. The level of cutaneous analgesia was at the third dorsal dermatome. When placed in the refrigerator he shivered vigorously above the waist line. There was no shivering below the waist line. (This patient is discussed further in the section on "Potency and Sexual Physiology.")

Anterior chordotomy, including section of the anterolateral column and at least the greater portion of the anterior column, eliminated the possibility of shivering below the section in 3 patients who were adequately tested. Shivering appears to be an ipsilateral phenomenon.

SUPERFICIAL AND DEEP REFLEXES

It has been our impression from the results of qualitative studies that the activity of abdominal and cremasteric reflexes has been neither significantly increased nor decreased after anterior chordotomy.

In a previous communication [3] one of us (O. H.) reported observations on deep reflexes and clonus. The results of a limited chordotomy, as indicated in figure 1, were considerably different from those of a more complete anterior chordotomy, as indicated in figure 2. The results led to the deduction that the anterior column plays an important role. The following conclusions are drawn:

Section of the anterior half of the cord results at most in transient flaccid paralysis and a longer-lasting loss of extensor tone or sustained antigravity reflex.

The descending extrapyramidal tracts, and in fact the anterior half of the cord, are not indispensable to normal strength and movement patterns in man. The tracts in the anterior column do appear to contribute to the sustained contraction of the antigravity muscles, such as is necessary in standing and walking. The loss of strength which follows anterior chordotomy is often a subjective complaint rather than an objective finding.

When the anterior half of the cord was divided, signs of upper motor neuron involvement, which characterize lesions of the pyramidal tract, did not appear during the period of observation, up to three years. It is assumed that in the performance of this type of chordotomy the pyramidal tracts, at least in some patients, were damaged sufficiently to have resulted in the upper motor neuron signs had the neural mechanism necessary for their development not been interrupted.

A mild injury of the pyramidal tracts with preservation of the anterior column is followed by acute development of hyperreflexia—hyperactive knee and ankle reflexes, ankle clonus and a Babinski sign. Involuntary resistance to flexion and extension of the foot and leg (spasticity) does not supervene.

Hence hyperreflexia may obtain independent of spasticity.

The acute development of hyperreflexia with the anterior column intact, in contradistinction to chronic development of hyperreflexia in spinal man, indicates a dual mechanism for so-called upper motor neuron signs. One mechanism operates through the agency of the anterior column, while the other is a purely spinal phenomenon.

We should like to add another observation concerning reflexes. After a complete transverse lesion of the cord, a withdrawal reflex often makes its appearance within a few days, but it may require weeks or months for the patellar or the achilles tendon reflex to reappear. After chordotomy, however, if there is a period of paralysis of the lower extremities, the patellar and the achilles tendon reflex reappear in a day or two. In a patient who maintained paralysis in one extremity for two weeks, there was never a semblance of the withdrawal reflex, but the patellar and achilles tendon reflexes were normal. We feel that these observations bear out a good prognosis for return of function and indicate an intact pyramidal tract.

REENFORCEMENT OF DEEP REFLEXES

Only a small group of patients appeared to be suitable for unequivocal determination of the effect of anterior chordotomy on the phenomenon of reenforcement. Patients who exhibited no ankle or patellar reflex, with and without reenforcement, were discarded. Patients were considered suitable when the reflex was absent without reenforcement and was present with reenforcement, as well as when the reflex was weak without reenforcement and unquestionably augmented by reenforcement. Reenforcement was occasioned in the usual manner by having the patient clasp his hands and pull.

CASE 16.—G. B., a white woman aged 41, complained of intractable pain, due to an inoperable carcinoma of the uterus.

On Dec. 16, 1941 bilateral anterior chordotomy was done at the first dorsal segment. The level of analgesia was at the fifth dorsal dermatome. The result was excellent, with only slight diminution in motor strength of the lower extremities.

Jan. 10, 1942: The patellar reflex was regarded as being 1 plus on both sides, with and without reenforcement. The achilles tendon reflex was absent on both sides without reenforcement and was 1 plus on both sides with reenforcement. These results were consistently obtained on several occasions.

CASE 17.—L. C., a white woman aged 40, complained of intractable pain due to an inoperable carcinoma of the uterus.

On Jan. 8, 1942 bilateral anterior chordotomy was done at the first dorsal segment. The level of analgesia was at the sixth dorsal dermatome. The result was excellent, with only mild diminution of motor strength in the lower extremities.

February 1: The patellar reflex was regarded as being 2 plus on both sides without reenforcement and was slightly augmented with reenforcement. The achilles tendon reflex was almost absent on both sides without reenforcement and was augmented to 1 plus with reenforcement. The results were consistent on a number of occasions.

CASE 18.—M. S., a white woman aged 46, complained of severe pain in the right upper extremity and the right side of the chest, due to carcinoma of the breast with metastases.

On Dec. 18, 1941 the posterior roots on the right side from the third cervical to the first thoracic segment inclusive were cut, and on December 27 an anterior chordotomy was done between the eighth cervical and the first thoracic root on the left side, as shown in figure 2.

On December 31 and Jan. 8, 1942 the patellar and achilles tendon reflexes were weak but equal on the two sides. Both reflexes were definitely augmented, and to an equal degree, by reenforcement on both the normal side and the side of operation.

The results for 3 suitable patients of anterior chordotomy done as shown in figure 2 indicate that this procedure does not abolish the effect of reenforcement on deep reflexes, particularly with respect to the achilles tendon reflex.

C. INFLUENCE ON POTENCY AND SEXUAL PHYSIOLOGY

Only a small percentage of patients could give adequate information concerning the effect of anterior chordotomy on sexual powers. We have selected a small group in which the results, we believe, may be accepted as directly due to this procedure. The information was obtained by letter or by follow-up examination during March 1942. The cases are briefly outlined, as follows:

CASE 19.—J. B., a man aged 42, had an anterior chordotomy, as shown in figure 2, on Jan. 29, 1940, for relief of gastric crises. The chordotomy was done bilaterally at the seventh cervical segment, and the level of analgesia reached the third dorsal dermatome. Erections and orgasm have been abolished up to the time of writing. The gastric crises never recurred.

CASE 7.—A. R., a man aged 52, had anterior chordotomy, as shown in figure 2, on Feb. 8, 1939 for relief of gastric crises. The chordotomy was done bilaterally at the second dorsal segment, and the level of analgesia reached the sixth dorsal dermatome. Erections and orgasm have been abolished to the time of writing. The gastric crises never recurred.

CASE 6.—H. T., a man aged 35, had anterior chordotomy, as shown in figure 2, on May 29, 1941, for relief of gastric crises. The chordotomy was done bilaterally at the first dorsal segment. A check-up examination, on March 12, 1942, showed that the level of analgesia was at the xiphoid process. Except for the thermanesthesia and analgesia, no abnormal neurologic signs could be elicited. The gastric crises were entirely relieved. He stated that he occasionally had psychologic erections, but they were only 50 per cent of normal. He did experience orgasms occasionally for eight months after operation, but they have been unattainable for the past two months. The functions of the bowel and bladder are unimpaired.

CASE 15.—A. S., a man aged 35, had anterior chordotomy, as shown in figure 2, on Dec. 20, 1939, in an attempt at relief of essential hypertension. The chordotomy was done bilaterally at the first dorsal segment, and the level of analgesia reached the sixth dorsal cutaneous segment. The patient stated in a letter that he experienced occasional erections, but "intercourse was not normal."

CASE 20.—J. J., a white man aged 39, had severe gastric crises. On Aug. 31, 1937 a complete bilateral anterior chordotomy was done at the second dorsal segment as shown in figure 3. The level of cutaneous analgesia was between the fifth and the sixth dorsal derma-

tome. The last check-up examination, made two years after operation, showed an excellent result, with complete elimination of gastric crises. Erection and orgasm were completely abolished by the chordotomy. (This patient has been reported on in greater detail in a previous report.[2])

CASE 21.—L. E., a woman aged 25, had anterior chordotomy, as shown in figure 2, on Oct. 10, 1939, in an attempt at relief of essential hypertension. The chordotomy was done bilaterally at the first dorsal segment. A check-up examination was made on March 14, 1942. Analgesia and thermanesthesia were complete to the tenth dorsal dermatome on the right side and only 50 per cent of normal from the toes to the tenth dorsal dermatome on the left side. Analgesia was not complete about the perineum. The patient has had intercourse a number of times since the operation, but orgasm has been completely abolished. Menstruation is normal, and she became pregnant and delivered a normal child after operation.

CASE 22.—A. G., a woman aged 50, had a modified chordotomy, as shown in figure 1, on May 11, 1939, in an attempt at relief of essential hypertension. The chordotomy was done at the second dorsal segment. Analgesia was complete to the twelfth dorsal dermatome on the left side and was partial to the region of the midthigh on the right side. The patient did not menstruate because the ovaries had been previously removed; after chordotomy orgasm was abolished.

CASE 23.—B. H., a woman aged 34, had a modified chordotomy, as shown in figure 1, on March 27, 1939, in an attempt at relief of essential hypertension. The chordotomy was done at the third dorsal segment; in addition, the anterior and posterior roots on both sides from

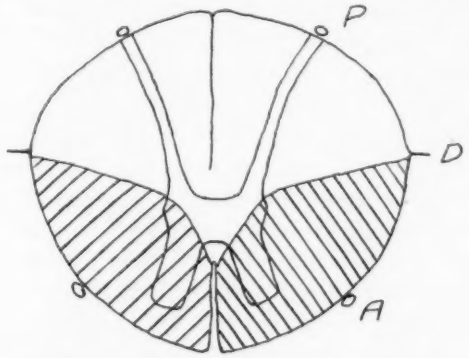

Fig. 3.—Diagrammatic representation of the manner in which the cord was sectioned in case 20.

the first to the third dorsal segment inclusive were cut. In addition to the expected sensory loss in the distribution of the first to the third dorsal dermatome, there was partial analgesia up to the level of the umbilicus. Menstruation was normal, but orgasm has been abolished since the operation.

CASE 2.—L. C., aged 35 (see section on "Girdle Pain"), had a modified anterior chordotomy, as shown in figure 1, and bilateral section of the anterior and posterior roots from the first to the fifth dorsal segment inclusive.

Frequent follow-up examinations were made over a period of three years. The possibility of orgasm was completely eliminated by the chordotomy.

From the results obtained with the foregoing 9 patients and from our other experience with chordotomy we feel that we can at least tentatively make the following derivations:

Bilateral anterior chordotomy is almost certain to abolish erection and orgasm in the male and orgasm in the female. The desire for intercourse is not abolished, but the ability of the male to carry out the sexual act is most likely to be lost. A modified chordotomy performed as illustrated in figure 1 is as effective in abolishing orgasm in the female as the type of chordotomy illustrated in figure 2. (Although no information was obtained in the case of a male patient after a modified chordotomy, it is reasonable to assume that the result would be comparable to that in the female patient.) Therefore it appears that the tracts which subserve the function of psychologically controlled erection and the sensation which accompanies

orgasm do not reside in the anterior column, but are probably located close to the gray matter in the anterolateral column. It also appears, with special reference to case 2, that the sensation which accompanies orgasm is not a modality of pain or temperature sense,[22] and certainly not a modality of touch sense. It is probably a specialized sensation, mediated by fibers localized deep toward the center of the cord in the anterolateral column. From what is known at present,[9] it can be said that in the male erection and the sensation of orgasm depend on the integrity of the sacral parasympathetic fibers, while ejaculation is a function of the sympathetic fibers (?). In the female the sacral parasympathetic fibers are necessary for the orgasm and the congestion that is comparable to erection. (We have no information on whether ejaculation may occur even though the sensation of orgasm is lost and vice versa, but the deficient erection following chordotomy makes the sexual act impossible anyway.) It is known, however, that erection and ejaculation may occur as a part of the mass reflex in spinal man. For the function to be psychologically controlled, however, and the orgasm to be sensually appreciated, the spinal connections with the brain must of course be intact. The significant point is that the afferent and efferent fibers in the cord which are related to these features of the sexual act must be rather well localized and fairly close together. They would constitute a parasympathetic tract. Voluntary control of micturition must be largely subserved by a parasympathetic tract also, but since the sexual function is so much more vulnerable than that of micturition, the two tracts must be separated, or in some way differently disposed.[23] (It is recognized that micturition is aided to a small extent by pyramidal control of striated muscle, while erection is purely an autonomic function.) It has been our impression that the function of defecation is somewhat less vulnerable than that of micturition after the performance of anterior chordotomy, but occasionally the reverse is true.

It was pointed out in a previous report [5] that thermoregulatory sweating was not at all diminished by chordotomy unless there was evidence of severe damage to the pyramidal tracts (on a spinal level). It was concluded that the sympathetic tracts which subserve this function were close to the pyramidal tracts, if not partly contained in them. Therefore it can be said with more certainty that the parasympathetic tracts in question and the sympathetic tracts which control sweating are sufficiently remote from each other that they are separable by an incision into the cord.

Menstruation has not been impaired after any type of anterior chordotomy. Patient 21 became pregnant after chordotomy and delivered a normal child. There was no departure from the normal mechanism of labor except that during the first stages uterine contractions were not accompanied by pain. Since analgesia was not complete about the perineum, particularly on the left side, she did experience pain when labor was well under way.

D. INFLUENCE ON THE VASCULAR SYSTEM

The cases of 4 patients are here presented on whom studies were made before and after chordotomy with respect to blood pressure, pulse, (respiration), electro-

22. Note that in this patient the analgesic zone did not present the pattern that results from a lesion involving the sacral segments. The analgesia was of a "stocking" pattern.

23. Simons (J. Urol. **48**:331-350 [Sept.] 1942), after studying bladder function, expressed the belief that the efferent tract subserving contraction of the bladder resides in the pyramidal tract. He stated that it is possible that the afferent impulses are transmitted not by the posterior column but by other columns, such as the spinothalamic tract. The spinothalamic tract does carry pain impulses from the bladder, but if a special afferent tract is required for normal bladder function, the restoration or preservation of the latter after anterior chordotomy would indicate that the special pathway does not reside in the spinothalamic tract.

cardiographic changes, circulation time, venous pressure, carotid sinus reflex and renal function, as well as cold pressor and glyceryl trinitrate tests.

CASE 15.—A. S., a white man aged 35, was first admitted on Nov. 1, 1939 with a history of high blood pressure for two years. He had had a light stroke in December 1938. He complained of headache, dizziness, blurring of vision, nosebleed, nocturnal dyspnea and precordial pain. (This patient is also considered in sections B and C.)

Examination.—The essential significant findings were hypertensive retinitis, without papilledema, and a blood pressure of 220 systolic and 155 diastolic.

Laboratory Studies.—Examination of the blood and urine gave normal results; the Wassermann reaction was negative.

The urea nitrogen of the blood measured 10.5 mg., the creatinine 1 mg. and the plasma proteins 6.61 mg. per hundred cubic centimeters; the basal metabolic rate was + 21 per cent.

A teleroentgenogram of the chest showed a normal condition, with no cardiac enlargement. Intravenous and retrograde pyelograms were normal. The spinal fluid was normal, with an initial pressure of 165 mm. of water when the patient was in a prone position.

During a cold pressor test the blood pressure rose from 196 to 214 systolic and from 130 to 142 diastolic. During a glyceryl trinitrate (nitroglycerin) test the blood pressure dropped from 204 to 188 systolic and from 138 to 124 diastolic.

Diagnosis.—The diagnosis was essential hypertension grade 3.

Chordotomy (Dec. 30, 1939).—Incisions were made between the sixth and the seventh cervical root on the left side and between the seventh and the eighth cervical root on the right side. The cataract knife was inserted into the cord about 1 mm. anterior to the dentate ligament and brought out about 2 mm. mesial to the line of the anterior roots. The level of analgesia reached to about the third dorsal dermatome on each side.

Result.—In addition to the results listed in the table, the patient was relieved of headache but continued to experience dizziness, particularly on arising in the morning.

CASE 22.—E. W., a white woman aged 35, for the past six years had experienced tachycardia, shortness of breath and occasional cyanosis when stooping or working hard. Frontal headaches were frequent and severe. For eight months there had been low abdominal pain, which was worse during the menstrual periods.

Examination.—The essential significant findings were moderate sclerosis of the retinal vessels, without papilledema, a faint systolic murmur over the mitral area and a blood pressure of 175 systolic and 115 diastolic. Chronic inflammatory pelvic disease accounted for the low abdominal pain.

Laboratory Data.—The blood and urine were normal, and the Wassermann reaction was negative. Urea nitrogen measured 10.5 mg. and creatinine 1 mg. per hundred cubic centimeters of blood. The intravenous pyelograms were normal. The basal metabolic rate was normal. The spinal fluid was normal, and the pressure was 125 mm. with the patient in the prone position.

Diagnosis.—The diagnosis was essential hypertension grade 3.

Chordotomy (March 7, 1940).—Sections were made on both sides at the first dorsal segment. The cataract knife was inserted a good 2 mm. anterior to the dentate ligament and brought out almost to the anterior median fissure. The patient made an uneventful recovery except for weakness of the bladder for five days. The level of analgesia was at the fifth dorsal dermatome, but the posterior aspect of the lower extremities from the buttocks down retained 50 per cent sensibility to pain. Evidently, the sections in the cord were begun slightly too far anteriorly.

Result.—In addition to the results listed in the table, the pelvic pain was abolished. Relief of the subjective symptoms was not striking.

CASE 19.—L. E., a white woman aged 25, was admitted to the medical service on July 31, 1939. She was known to have had high blood pressure for three years. She complained of nosebleed for six years and headache and swelling of the ankles for two years.

Examination.—The essential significant findings were mild sclerosis of the retinal vessels, without papilledema, and a blood pressure of 180 systolic and 140 diastolic. Early pregnancy was discovered after the chordotomy.

Laboratory Studies.—The blood and urine were normal; the Wassermann reaction was negative, and the chemical constituents of the blood were within normal limits. The spinal fluid was normal, with a pressure of 130 mm. of water with the patient in the prone position.

Diagnosis—The diagnosis was essential hypertension grade 3.

Blood Pressure (Averages)

	Preoperative	Postoperative			
		3 Days	3 Mo.	6 Mo.	
1	250/135	160/100	142/90	210/100	
2	185/115	110/70	110/74	180/100	190/110 (17 mo.)
3	210/140	110/60	120/80	150/94	160/110 (20 mo.)
4	200/135	130/80	168/100	180/110	175/105 (12 mo.)

Pulse Rate

1	86	90	76	76
2	86	88	80	80
3	80	80	72	72
4	80	75	75	75

Respiration

There was no significant change in respiration after anterior chordotomy

Electrocardiogram

Electrocardiograms were taken from the 4 patients before and from ten weeks to three months after chordotomy. All the records were normal.

	Circulation Time, Sec.* (Arm to Tongue)		Venous Pressure, Mm. of Venous Blood †	
	Preoperative	Postoperative	Preoperative	Postoperative
1	14	14	35	30
2	17	17	170	150
3	14.4	13	145	150
4	12	10	120	110

Carotid Sinus Reflex ‡

		Preoperative		Postoperative		
		Before	After	Before	After	
1	Blood pressure, mm.	198/126	186/118	158/92	140/88	5 wk.
	Pulse	100	100	84	80	
2	Blood pressure, mm.	178/110	160/104	140/96	132/84	10 wk.
	Pulse	88	80	84	80	
3	Blood pressure, mm.	170/116	156/92	130/80	116/72	3 mo.
	Pulse	88	80	84	80	
4	Blood pressure, mm.	184/110	156/100	180/104	156/100	2 mo.
	Pulse	90	90	90	72	

* The test for circulation time was carried out with a solution of 42 Gm. of magnesium sulfate, 16 Gm. of calcium gluconate, 0.9 Gm. of sodium chloride and 1 mg. of copper sulfate in 100 cc. of distilled water. When this solution is injected intravenously it produces a sensation of warmth throughout the body and causes a flash of heat to be experienced successively in the throat, the perineum, the hands and the feet. The time elapsing between injection of the solution and detection of the reaction is known as the circulation time.

† Venous pressure was measured by puncturing the antecubital vein with a no. 22 needle, to which was connected a manometer. The vein was placed on a level with the heart, and the readings represent millimeters of venous blood.

‡ Basal readings were taken. The carotid sinus was then massaged on one side for fifteen seconds, and readings were taken again. Stimulation of the carotid sinus was done on the same side before and after operation.

It is not surprising that chordotomy had little influence on the carotid sinus reflex. The reflex is predominantly depressor. The afferent fibers enter the medulla with the glossopharyngeal nerve, and the efferent fibers course with the vagus nerve. We tested the reflex in 2 patients before and after section of the anterior and posterior dorsal roots from the first to the fifth dorsal segment inclusive on both sides, as well as after cervicodorsal ganglionectomy, and in 1 patient after a complete transverse lesion at the sixth cervical segment of the cord. In all the patients the reflex was manifested to at least the degree exhibited in the table.

Data on Vascular Reactions of Four Patients with Anterior Chordotomy—Continued

Renal Function Test (Urea Clearance, %)

	Preoperative	Postoperative
1	100	100
2	80	85
3	67	83
4	97	100

Cold Pressor Test §

	Preoperative Blood Pressure, Mm.		Postoperative Blood Pressure, Mm.		
	Basal	After 1 Min.	Basal	After 1 Min.	
1	...	...	...	...	
2	190/130	220/136	180/120	190/120	
3	180/110	200/110	110/64	134/80	(1 mo.)
4	208/110	238/144	188/110	218/114	(1 mo.)

Glyceryl Trinitrate (Nitroglycerin) Test ‖

	Preoperative Blood Pressure, Mm.		Postoperative Blood Pressure, Mm.		
	Basal	Lowest Pressure	Basal	Lowest Pressure	
1	...	...	...	...	
2	180/120	157/120	150/100	120/100	(50 days)
3	184/110	144/98	150/100	50/?	(5 mo.)
4	200/114	166/114	194/112	140/94	(1 mo.)

§ Several basal determinations of blood pressure were made. A hand was immersed in ice water and readings were taken in thirty and sixty seconds. The hand was then taken out and a reading taken in five minutes.

‖ Several basal determinations of blood pressure were made. Then 5 drops of tincture of glyceryl trinitrate was placed on the tongue, and pressures were taken each minute for four minutes. The procedure was repeated after application of 7 drops of the tincture, and so on, the dose being increased up to 12 drops. In this way the maximum lowering of blood pressure that could be obtained with a reasonable dose of glyceryl trinitrate was determined.

Chordotomy (Oct. 10, 1939).—The sections were made at the first dorsal segment on both sides. A cataract knife was inserted anterior to the dentate ligament and brought out mesial to the line of the anterior roots. The level of analgesia was at the fifth dorsal dermatome, but the perineum and the right buttock were not completely analgesic.

On April 19, 1940 the patient delivered a normal child by a normal mechanism of labor. During the early stage of labor uterine contractions were not painful, but during the last stage she experienced considerable pain with the contractions and in the perineum, but only on one side. The highest level of blood pressure, which occurred on complete dilatation of the cervix, was 230 systolic and 145 diastolic. Additional results are listed in the accompanying table.

Results.—At a check-up examination eight months after operation, the patient stated that headache had been practically eliminated and the ankles no longer swelled.

Case 20.—A. G., a white woman aged 49, was admitted on April 26, 1939, with the complaint of dizzy spells and shortness of breath for five years.

Examination.—The essential findings were arteriosclerotic changes in the retinal vessels, without papilledema, and a blood pressure of 200 systolic and 135 diastolic. She also presented prolapse of the uterus.

Laboratory Data.—Examination of the blood and urine, the Wassermann test and chemical studies of the blood gave normal results. The spinal fluid was normal, with a pressure of 160 mm. of water when she was in the prone position.

Diagnosis.—The diagnosis was essential hypertension grade 3.

Chordotomy (May 11, 1939).—With local anesthesia, sections were made at the second dorsal segment of the cord on both sides in the following manner: A cataract knife was

inserted immediately anterior to the dentate ligament and to a depth of about 4 mm., as indicated in figure 1. Immediately after the sections were made, the blood pressure was 180 systolic and 110 diastolic. One hour later the pressure was 120 systolic and 80 diastolic and the pulse rate 65 per minute, without any evidence of shock. Analgesia on the left side reached the groin. On the right sensibility to pain was about 50 per cent to the midthigh.

Results.—At a check-up examination two months after operation the patient denied having headache, shortness of breath or palpitation, although the blood pressure at this time was 215 systolic and 135 diastolic. Other results of examination are presented in the table.

E. EFFECT OF SECTION OF LISSAUER'S TRACT

The results of section of Lissauer's tract have been reported.[24] Section of the tract in 9 cases has shown that this tract accounts for the discrepancy between the level at which the section of the anterior cord is made and the upper level to which the analgesia reaches. A section of the tract in the thoracic region results in analgesia and thermanesthesia in a band three to five segments wide on the same side. When anterior chordotomy is done at the first dorsal segment on one side and Lissauer's tract cut at the same segment on the opposite side, analgesia reaches the axilla (first dorsal segment) on the side of section of Lissauer's tract. Hence this additional procedure serves to obtain a high level of analgesia up to and including the first dorsal dermatome. Section of Lissauer's tract in the cervical portion of the cord in 2 patients has not resulted in analgesia of the upper extremity.

CONCLUSIONS

Anterior chordotomy in our patients has not influenced thermoregulatory sweating and has had little influence on the known arteriolar reactions, as indicated by capillary flushing and reflex vasodilatation from heating of the body. The inference, therefore, is that the anterior chordotomy does not sever the central sympathetic connections to any significant degree. Anterior chordotomy also caused relatively little alteration in the reaction of blood pressure to the cold pressor test and to glyceryl trinitrate (nitroglycerin). The average blood pressures, however, were reduced considerably for three to six months.

Anterior chordotomy does sever central parasympathetic connections, especially those related to erection and the sensation of orgasm. The sensation of orgasm, however, appears to be a special sense, not mediated by the spinothalamic tract. Bowel and bladder function are much less impaired, often only transiently.

Visceral pain is mediated in the spinothalamic tract and is eliminated by chordotomy, but the differences in visceral topography must be taken into consideration. Hence we believe the optimum location for performance of the routine chordotomy is at the first dorsal segment and that the section should completely interrupt the spinothalamic tract. Unilateral chordotomy may not completely abolish pain in the testicles and the renal pelvis on the analgesic side. This indicates a partial bilateral representation for these viscera.

Anterior chordotomy abolishes shivering, various forms of girdle pain and itching, but not tickle. Our studies lead us to believe that itch is mediated by pain fibers and is a modality of the basic sensation of pain. Chordotomy does not abolish the phenomenon of reenforcement of deep reflexes.

Anterior chordotomy at the first dorsal segment combined with section of Lissauer's tract ordinarily brings the level of analgesia to the first dorsal dermatome and is useful in abolishing pain high in the chest.

College of Medicine, State University of Iowa.

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METABOLIC STUDIES ON EPILEPTIC PATIENTS RECEIVING AZOSULFAMIDE AND PHENOBARBITAL

MANDEL E. COHEN, M.D.
BOSTON

CAPTAIN FREDERICK S. COOMBS
MEDICAL CORPS, ARMY OF THE UNITED STATES

STANLEY COBB, M.D.
BOSTON
AND
LIEUTENANT COLONEL JOHN H. TALBOTT
MEDICAL CORPS, ARMY OF THE UNITED STATES

Azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) has been demonstrated to exhibit anticonvulsant action in patients with epilepsy.[1] Associated with the anticonvulsant effect, alterations in the concentration of chemical constituents of the serum were described. These included a decrease in the carbon dioxide content of the serum, a decrease in the carbon dioxide–combining power of the serum and an elevation in serum chlorides.[1b] The purpose of the present study was to determine in more detail the nature of the metabolic changes associated with ingestion of azosulfamide, as well as with phenobarbital, a drug with well known anticonvulsant properties.

PLAN OF STUDY

Two patients with epilepsy were selected for this study whose seizures were known to have diminished during administration of azosulfamide (cases 3 and 2[1b]). One patient suffered from many petit mal attacks daily; the other, from severe generalized convulsions. The general plan of the study was as follows: After a preliminary period of observation in the psychiatric ward, the patients were transferred to the metabolism ward for metabolic studies. They were given a constant amount of food and fluid daily; complete collections were made of the urine and stools excreted, and determinations were made of the daily excretions of various constituents. The concentrations of various constituents of the blood and serum were determined. After a control period in which no drugs were given, azosulfamide, phenobarbital and ammonium chloride were each given for a period. A final control period without the administration of any drugs concluded the study.

METHODS

The patients were given daily a neutral diet (protein, 86.5 Gm.; carbohydrates, 217.5 Gm., and fat, 75.6 Gm., plus 2 Gm. of sodium chloride, chemically pure, the total number of calories amounting to 1,885) during the periods of study in the metabolism ward. The food was purchased in five day lots and analyzed according to the methods of Atchley and associates.[2] One half of a duplicate day's diet from each lot was weighed, dried and analyzed. The urine was collected under toluene and kept in the ice chest. It was partitioned and analyzed every twenty-four hours. The stools, which were collected in periods corresponding to the various periods of

From the Departments of Medicine and Neuropathology, Harvard Medical School, and the Medical and Psychiatric Clinics of the Massachusetts General Hospital.

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drug therapy or of the control periods, were dried and analyzed in a manner similar to that for the diets. Samples of drugs ingested were analyzed with the diet.

Arterial blood was analyzed for oxygen capacity,[3] cell volume per cent[4] and oxygen saturation.[3] Arterial serum was analyzed for concentrations of total fixed base,[5] sodium,[6] potassium,[7] chloride,[8] phosphate,[9] urate,[10] protein,[11] nonprotein nitrogen,[12] carbon dioxide content[3] and partial pressure of carbon dioxide,[13] and the p_H was calculated according to the Henderson-Hasselbalch equation.[14] A partial summary of the methods used has been described before.[15]

The daily volume of urine was measured, and the urine was analyzed for the daily excretion of sodium,[6] potassium,[7] calcium,[16] total base,[5] ammonia,[17] chloride,[18] titratable acid,[19] phosphate[17] and total nitrogen,[11] and the p_H was calculated.[20] Stools were analyzed for the daily content of sodium,[6] potassium,[7] calcium,[16] chloride,[8] phosphate[9] and nitrogen.[11] From the analyses of the diet, drugs, urine and stools, data on the metabolic balance were calculated.[21] The patients were weighed daily.

PROCEDURE

CASE 1.[22]—A 20 year old woman had suffered many brief lapses of consciousness and occasional convulsions for twelve years. The spells consisted of staring, change in color of the face and sometimes flickering of the eyelids. She was aware of each spell and was able to count them accurately, as corroborated by observations of nurses and physicians and by electroencephalographic tracings. This patient had previously been noted to become free of spells for nine days with azosulfamide therapy.[1b] During control periods without medication and with administration of placebos she had an average of 10 spells per day.

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22. Cases 1 and 2 have been reported in more detail in a previous publication.[1b] Case 1 in this study is case 3 in that report, and case 2 is case 2.

The metabolic study of this patient was divided into eight periods.

Preliminary Period.—During this period the patient was hospitalized in the psychiatric ward. A control interval, during which the daily average of spells was established at 10 a day, was followed by an interval of placebo medication. Azosulfamide was administered, and when a definite effect had been demonstrated, the placebo was again substituted for the drug, with return of the spells. Administration of the placebos was then discontinued. During this time observations were made on the carbon dioxide content and the carbon dioxide–combining power of both venous and arterial serum [3] and on the chloride content,[8] the p_H [23] and the sulfanilamide concentration [24] of venous blood. The patient was admitted to the metabolism ward for further study.

Period 1 (control period, four days).—The patient received a constant analyzed diet. The intake and the output of fluid were measured. The blood was analyzed. All the urine and stools were collected and analyzed. Values for metabolic balance were calculated. No medication was used. The spells were counted.

Period 2 (azosulfamide).—The same procedure was followed as in the control period. Azosulfamide, 10 Gm. per day, was administered.

Period 3 (control period).—The same procedure was followed as in period 2, but with no medication.

Period 4 (control period).—The same procedure was followed as before, with omission of metabolic balance studies. No medication was employed.

Period 5 (ammonium chloride).—The same procedure was followed as in period 2, but with administration of ammonium chloride in doses of 5 Gm. the first two days and 8 Gm. the last two days. The purpose of the study during this period was to determine whether metabolic changes similar to those observed during administration of azosulfamide would induce a similar anticonvulsant effect.

Period 6 (control period).—The same procedure was followed as in the preceding period except for omission of the balance studies. No medication was employed.

Period 7 (phenobarbital).—The same procedure was followed as in period 2, but with administration of phenobarbital, 0.2 Gm. daily. The purpose was to determine whether another drug with anticonvulsant properties would induce metabolic changes similar to those with azosulfamide.

Final Period.—Further studies, similar to those in the preliminary period, were conducted in the psychiatric ward. For details see the previous report.[1b]

CASE 2.—A 16 year old white girl had severe epilepsy. With her usual dose of phenobarbital she had an average of about 1 generalized convulsion a day. When azosulfamide was administered, convulsions were reduced, there being 4 seizures in thirty-one days. Azosulfamide was withdrawn, and on the third day there were 6 violent convulsions. The patient was comatose and could not be roused between convulsions. Azosulfamide was administered through a stomach tube, and when consciousness was restored more of the drug was given by mouth. Then followed a period during which the patient received a daily dose of 12 Gm. of azosulfamide and was practically free of convulsions. During this period the patient was transferred to the metabolism ward. The study of this patient was divided into four periods.

Preliminary Period.—The patient was observed in the psychiatric ward while she was receiving phenobarbital (½ grain [0.032 Gm.] daily), azosulfamide (average 10 Gm. daily), no medication and then azosulfamide (12 Gm. daily). The arterial and the venous blood were analyzed for carbon dioxide content, carbon dioxide–combining power, sulfanilamide concentration and p_H.

Period 1 (azosulfamide).—The same procedure as that employed in case 1 was followed, 12 Gm. of azosulfamide being administered daily.

Period 2 (phenobarbital).—The same procedure was followed as in period 1. Phenobarbital, 0.1 and then 0.2 Gm. was administered daily.

Final Period.—Further studies were conducted in the psychiatric ward, as in the preliminary period. For details see the previous report.[1b]

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TABLE 1.—*Data on Preliminary Period in Case 1*

Day	No. of Spells	Treatment	Arterial Blood				Venous Blood					Alveolar Carbon Dioxide, Mm. of Mercury	Ventilation, Liters per Min.
			Carbon Dioxide Content, Vol. %	Chloride, Cc. N/10 Chloride per 100 Cc.	p_H	Sulfanilamide, Mg. per 100 Cc.	Carbon Dioxide Content, Vol. %	Carbon Dioxide-Combining Power, Vol. %	Chloride, Cc. N/10 Chloride per 100 Cc.	p_H	Sulfanilamide, Mg. per 100 Cc.		
8	22	None	....	.....	....	...	....	54.2	106.1	....	0	33.3	8.27
11	12	None	....	.....	....	...	....	50.9	108.2	....	0		
15	7	None	....	.....	....	...	....	55.9	108.1	....	0	35.4	8.95
18	7	None	....	.....	....	...	....	59.8	106.8	7.48			
22	25	None	....	.....	....	...	....	64.0	104.4				
25	8	None	....	.....	....	...	....	52.8	106.3	7.48			
30	8	None	....	.....	....	...	....	56.1	107.1	7.42			
36	8	Placebo	....	.....	....	...	....	56.4	106.7				
39	4	Azosulfamide	....	.....	....	...	....	53.4	106.1				
44	0	Azosulfamide	....	.....	....	...	....	45.5	113.0	7.38	3.2		
46	0	Azosulfamide	....	.....	....	...	....	35.0	111.5	7.42	2.2		
49	0	Placebo	....	.....	7.48	...	....	....	.....	7.43			
50	1	Placebo	....	.....	....	...	....	54.0	107.2	....	Trace		
53	5	Placebo	....	.....	....	...	....	54.9	105.8	7.52	Trace		
57	11	Placebo	....	.....	....	...	....	....	.....	7.52			
63	14	None	52.0	106.8	....	...	....	....	.....	....	...	36.9	
67	1	Azosulfamide	51.8	105.5	7.38								
71	0	Azosulfamide	37.9	111.7	7.31	2.9	....	....	.....	7.45	...	31.6	
75	36	None	48.9	108.3	7.42								
79	18	None	49.5	108.8	7.32								
83	9	Sulfanilamide	40.0	113.6	7.32								
91	0	None	51.6	106.0									
109	0	Sulfanilamide	....	.....	....	...	48.6	....	107.6	7.47	2.5		
111	0	Azosulfamide	....	.....	....	...	....	....	.....	....	2.0		
114	66	None											
115	40	None	....	.....	....	...	....	57.4	106.7	7.50	Trace		
118	0	Azosulfamide											
119	0	Azosulfamide	....	.....	....	...	52.2	....	112.0	7.40	4.0		
122	0	Azosulfamide	....	.....	....	...	54.5	....	109.4	7.47	Trace		
126	37	None	....	.....	....	...	....	58.8	104.4	7.47	0		
129	8	None	....	.....	....	...	60.6	....	106.1	7.48	0		
134	0	Phenytoin	....	.....	....	...	56.2	....	107.1	7.45	0		
136	0	Phenytoin	....	.....	....	...	57.6	....	.....	7.45			
140	12	Phenytoin	....	.....	....	...	57.9	....	107.6	7.43			
143	27	Phenytoin	....	.....	....	...	59.2	....	110.0	7.48			
147	80	Phenobarbital	....	.....	....	...	59.7	....	107.0	7.48			
150	2	Phenobarbital	....	.....	....	...	61.1	....	105.9	7.40			
154	1	Phenobarbital	....	.....	....	...	59.8	....	95.9	7.47			
157	0	Phenobarbital	....	.....	....	...	56.3	....	101.5	7.45			
162	0	Phenobarbital	....	.....	....	...	56.9	....	104.8	7.47			

RESULTS

CASE 1.—*Preliminary Period.*—The number of spells averaged 10 per day when no medicine or placebo was given. The patient became free of spells when azosulfamide was administered. When the placebo was again substituted, the spells returned. The patient was free of spells for ten consecutive days, the seizures returning on the third day after cessation of administration of azosulfamide.

Coincident with the administration of azosulfamide there were a decrease in the carbon dioxide–combining power, an increase in the concentration of chlorides and a decrease in p_H of the serum. The highest concentration of sulfanilamide in the blood was 3.2 mg. per hundred cubic centimeters (table 1).

Period 1 (control period).—During this period 7, 14, 12 and 8 spells were recorded on successive days. The concentration of constituents of the arterial blood showed no abnormalities (table 2). Urinary constituents presented no unusual trend (table 3). There was a positive potassium balance of 11.7 milliequivalents daily for the period (table 4). The balances of sodium, calcium, chloride and phosphate were not remarkable.

Period 2 (azosulfamide).—The spells numbered 5, 1, 0 and 0 on successive days. The sulfanilamide level of the blood was 2.9 mg. per hundred cubic centimeters. Determination of the concentration of constituents of the serum during this period showed an increase in chloride and a decrease in carbon dioxide content, carbon dioxide tension and p_H (table 2). Analysis of urinary constituents revealed a rise in p_H, an increase in excretion of sodium and total base, a decrease in excretion of calcium, a decrease in excretion of ammonia and an increase in excretion of chloride (table 3). There were a positive daily calcium balance of 12.8 milliequivalents and a negative daily chloride balance of 35.6 milliequivalents (table 4).

Period 3 (control period).—The spells numbered 0, 0, 0 and 2 on successive days. The serum showed a rise in the p_H to 7.42, a decrease in concentration of chlorides and a rise in the carbon dioxide content (table 2). Analysis of urinary constituents revealed a decrease in p_H, a decrease in excretion of sodium, potassium and total base, an increase in excretion of ammonia and a decrease in the excretion of chloride (table 3). Calculations of metabolic balances showed a daily positive potassium balance of 25 milliequivalents, a daily negative sodium balance of 11.7 milliequivalents and a daily positive calcium balance of 10.2 milliequivalents (table 4).

Period 5 (ammonium chloride).—The spells numbered 18, 15, 6 and 11 on successive days. Determination of the concentration of constituents in the blood showed a decrease in fixed base, sodium and chloride and a decrease in carbon dioxide content and p_H, with a slight decrease in carbon dioxide tension (table 2). Analysis of the daily urine revealed a decrease in p_H, an increase in excretion of potassium, an increase in excretion of total base, an increase in excretion of ammonia and an increase in excretion of chloride and titratable acid (table 3).

Calculations of metabolic balances showed a daily positive chloride balance of 23.2 milliequivalents and a daily positive nitrogen balance of 5.9 Gm. (table 4).

Period 7 (phenobarbital).—The spells numbered 19, 1, 0 and 0 on successive days. There was a rise in the concentration of urates (table 2) in the blood. Urinalysis revealed a decrease in the daily excretion of potassium and total base (table 3). There were a daily positive potassium balance of 16 milliequivalents and a daily positive calcium balance of 16.8 milliequivalents (table 4).

TABLE 2.—*Observations on Arterial Blood*

Date, 1939	Whole Blood: Oxygen Capacity, mM. per Liter	Whole Blood: Cell Volume, %	Whole Blood: Oxygen Saturation, %	Serum: Total Fixed Base, mEq. per Liter	Serum: Sodium, mEq. per Liter	Serum: Potassium, mEq per Liter	Serum: Chloride, mEq. per Liter	Serum: Phosphate, Mg. per 100 Cc.	Serum: Urate, Mg. per 100 Cc.	Serum: Protein, Gm. per 100 Cc.	Serum: Nonprotein Nitrogen, Mg. per 100 Cc.	Serum: Total Carbon Dioxide, mM. per Liter	Serum: p_H	Serum: Arterial Carbon Dioxide Tension, Mm. of Mercury
							Case 1							
March 21	....	....	....	151.3	139.5	4.3	106.8	3.4	4.1	6.4	30	23.2	....	....
March 25	7.16	0.36	98.0	150.1	139.5	5.1	105.5	...	4.3	5.9	29	23.1	7.38	38.0
March 29	7.05	0.36	....	149.3	138.1	4.1	111.7	...	4.3	6.0	27	16.9	7.31	32.0
April 2	7.00	0.36	96.7	147.8	138.0	4.7	108.3	...	4.7	6.2	..	21.8	7.42	32.7
April 6	7.08	0.36	96.5	150.2	140.5	4.9	108.8	...	4.3	5.9	..	22.1	7.32	36.2
April 10	6.86	0.36	96.5	143.6	134.3	4.5	113.6	...	4.4	5.7	..	18.0	7.32	33.1
April 18	....	0.37	....	148.9	138.1	...	106.0	...	5.3	6.3	..	23.0	....	....
							Case 2							
May 11	7.17	0.36	97.4	147.8	136.2	4.5	108.9	...	...	6.1	..	18.8	7.35	33.0
May 15	7.10	0.36	95.5	147.8	136.0	5.4	110.5	...	...	6.3	..	19.5	7.39	31.2
May 19	7.17	0.36	95.3	148.2	137.6	4.5	104.8	...	...	6.0	..	26.3	7.37	43.8
May 23	....	....	....	147.0	137.0	4.9	102.6	...	...	6.3	..	26.5	....	....

March 20, 1939

Phenolsulfonphthalein Time, Min.	Percentage
15	26
30	15
60	22
120	16
Total	79

March 29, 1939

	Amount per 100 Cc.
Total hemoglobin	7.66 Gm.
Methemoglobin	0.47 Gm.
Sulfhemoglobin	0.25 Gm.
Sulfanilamide	2.9 mg.

TABLE 3.—*Daily Observations on Urinary Constituents in Case 1*

Date, 1939	Volume, Cc.	p_H	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.	Total Base, mEq.	Ammonia, mEq.	Chloride, mEq.	Titratable Acid, mEq.	Phosphate, Gm.	Total Nitrogen, Gm.	Urate, Mg.	Body Wt., Kg.
Period 1													
March 21-22	1,610	6.8	122.4	74.0	11.6	256.6	33.7	129.4	16.4	1.07	12.88	780	47.3
22-23	1,930	6.8	138.0	67.6	14.4	261.0	33.7	144.5	20.0	0.94	11.90	620	47.1
23-24	1,570	6.4	99.2	68.9	11.0	225.4	30.9	111.5	26.8	1.07	12.30	640	46.9
24-25	1,570	6.4	91.6	64.0	10.4	223.0	29.3	101.3	24.4	1.06	11.82	520	46.9
Period 2													
March 25-26	1,630	7.4	145.6	87.0	5.5	283.4	17.8	110.8	....	1.16	12.24	650	46.1
26-27	1,960	8.0	223.6	64.6	11.0	348.6	13.3	158.8	....	1.09	10.68	550	47.4
27-28	1,790	7.6	195.3	90.0	9.6	318.0	18.8	178.6	....	1.01	9.94	520	47.3
28-29	1,880	7.6	200.9	58.0	5 6	324.2	25.5	163.0	....	0.99	10.68	520	47.2
Period 3													
March 29-30	1,690	6.4	132.9	42.4	15.9	268.4	42.0	135.5	33.0	1.08	11.16	...	46.9
30-31	2,080	5.8	127.0	38.6	16.0	246.8	56.2	78.6	30.5	0.89	11.44	...	46.7
31-April 1	1,910	5.6	102.6	38.4	14.9	229.4	56.6	128.5	33.2	0.93	7.96	...	46.8
1-2	1,770	5.9	96.4	51.2	12.5	220.8	40.8	114.3	29.4	0.94	7.64	...	46.9
Period 4													
April 2-3	1,820	6.1											
3-4	1,630	6.4											
4-5	1,800	6.6											
5-6	1,760	6.0											
Period 5													
April 6- 7	1,660	5.2	108.2	84.4	10.0	256.4	46.0	162.0	48.0	1.15	8.10	600	47.1
7- 8	1,990	5.0	126.6	92.0	12.3	290.8	57.8	206.8	47.8	1.14	7.74	390	46.9
8- 9	1,900	5.1	97.8	111.6	15.3	315.0	87.2	236.8	50.8	1.29	8.44	336	46.7
9-10	1,880	5.2	95.4	94.8	7.7	318.8	110.0	241.0	48.0	1.27	7.88	218	46.6
Period 6													
April 10-11	1,860	5.2	.....	....	....	232.6	107.0	.....	41.4				
11-12	1,900	5.9											
12-13	1,780	6.6											
13-14	2,010	6.8											
Period 7													
April 14-15	1,660	6.1	102.1	65.6	9.3	213.6	30.6	112.8	30.0	1.05	7.26	...	46.5
15-16	1,860	6.3	101.8	69.4	9.9	208.6	29.5	110.0	29.0	1.08	12.90	...	46.6
16-17	1,890	6.8	111.4	71.2	9.9	231.0	26.4	117.0	21.0	0.97	6.96	...	46.6
17-18	1,620	6.4	86.8	62.8	12.7	202.0	29.5	95.0	24.6	0.89	10.74	...	46.5

TABLE 4.—*Summary of Data on Metabolic Balance in Case 1*

	Constituent					
	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.	Chloride, mEq.	Phosphate, Gm.	Nitrogen, Gm.
Period 1 (Control)						
Intake	454	361	208	467	5.88	54.8
Output						
Urine	451	275	47	487	4.14	48.9
Stool	2.8	39.8	182.9	5.3	2.01	5.1
Daily balance	—0.0	+11.7	—5.2	—6.1	—0.06	+0.2
Period 2 (Azosulfamide)						
Intake	765	361	245	471	4.88	58.6
Output						
Urine	765	300	32	611	4.25	43.5
Stool	8.3	62.4	162.0	2.1	1.33	4.2
Daily balance	+18.0	—0.3	+12.8	—35.6	+0.07	+2.7
Period 3 (Control)						
Intake	420	338	231	434	5.78	53.0
Output						
Urine	459	171	58	457	3.84	38 0
Stool	8.0	64.2	131.7	7.2	1.23	3.5
Daily balance	—11.7	+25.7	+10.2	—7.5	—0.17	+2.8
Period 5 (Ammonium Chloride)						
Intake	438	361	213	945	5.82	59.8
Output						
Urine	428	383	45	847	4.85	32.1
Stool	1.0	32.4	182.3	5.3	1.79	3.8
Daily balance	+2.2	—4.2	—4.5	+23.2	—0.18	+5.9
Period 7 (Phenobarbital)						
Intake	433	359	238	460	5.98	54.9
Output						
Urine	402	269	42	435	3.99	37.8
Stool	0.1	30.1	128.8	2.4	1.37	2.3
Daily balance	+7.7	+16.0	+16.8	+5.5	+0.15	+3.7

TABLE 5.—*Data on Preliminary Period in Case 2*

Day	No. of Spells	Treatment	Arterial Blood: Carbon Dioxide Content, Vol. %	Arterial Blood: Chloride, Cc. N/10 Chloride per 100 Cc.	Arterial Blood: p_H	Arterial Blood: Sulfanilamide, Mg. per 100 Cc.	Venous Blood: Carbon Dioxide-Combining Power, Vol. %	Venous Blood: Chloride, Cc. N/10 Chloride per 100 Cc.	Venous Blood: p_H	Venous Blood: Sulfanilamide, Mg. per 100 Cc.
3	1	Phenobarbital	....	.....	....	...	56.4	104.3	7.38	
5	3	Phenobarbital	....	.....	....	...	....	109.2	7.48	
12	0	Phenobarbital	....	.....	7.55					
23	2	Phenobarbital	56.8	.....	7.55	...	54.6	109.4		
26	0	Azosulfamide	49.1	.....	7.48	...	49.9	107.6	....	3.4
30	0	Azosulfamide	45.3	.....	7.53	...	....	106.4	....	3.9
33	1	Azosulfamide	....	.....	7.42	...	....	.....	....	3.6
37	0	Azosulfamide	44.5	.....	7.47					
40	0	Azosulfamide	44.8	104.6	7.50	4.6				
44	0	Azosulfamide	44.2	108.0	7.40	3.7				
47	0	Azosulfamide	46.8	108.3	7.48	5.2				
51	0	Azosulfamide	43.6	.....	7.53	4.6				
55	0	Azosulfamide	46.1	.....	7.48					
74	1	Azosulfamide	41.6	108.9	7.35					
78	0	Phenobarbital	43.7	110.5	7.39					
82	1	Phenobarbital	58.9	104.8	7.37					
86	0	Phenobarbital	59.4	102.6						
100	0	Azosulfamide	43.1	.....	7.53	6.4				
110	0	Azosulfamide	....	.....	7.55					
117	0	Azosulfamide	....	.....	....	7.0				
131	0	Azosulfamide	43.1	112.3	7.55	6.4				

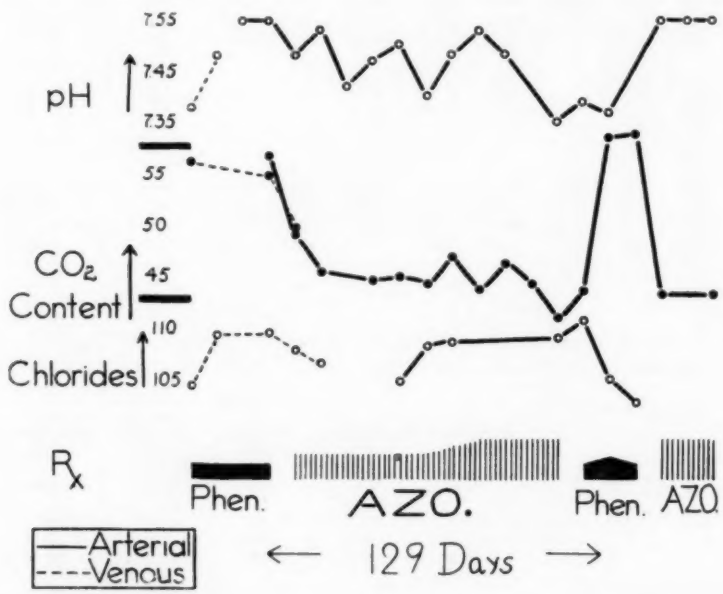

Chart 1.—Lowered carbon dioxide content and elevated chloride content of the serum with administration of azosulfamide. The values for arterial blood are indicated by solid lines; those for venous blood, by dotted lines. The entire period of study represented by the chart was one hundred and twenty-nine days.

CASE 2.—*Preliminary Period.*—During this period convulsions diminished during the administration of azosulfamide, increased when the drug was withdrawn and again decreased when the drug was readministered. There were a decrease in carbon dioxide content and a slight rise in the chlorides of the serum (table 5; chart 1).

In the third week of administration of azosulfamide the patient was transferred to the metabolism ward for determination of the effects of a more prolonged administration of the drug than was employed in the first case.

Period 1 (azosulfamide).—Three convulsions occurred in this period. Determination of the concentrations of constituents of the serum showed that the carbon

dioxide content, the carbon dioxide tension and the p_H were decreased (table 2). There was a greater urinary excretion of sodium and of chlorides (table 6) in this period than in the following period. There was a positive daily potassium balance of 14.1 milliequivalents, a negative daily sodium balance of 17.9 milliequivalents and a negative daily chloride balance of 87.2 milliequivalents (table 7).

Interval Period.—The number of convulsions rose to 5 daily when azosulfamide was withdrawn, despite administration of phenobarbital. The muscular activity during the convulsions and urinary incontinence prevented studies of metabolic balances.

Period 2 (phenobarbital).—There was 1 convulsion in this period. There was no change in the concentration of constituents of the blood and serum. The excre-

TABLE 6.—*Daily Observations on Urinary Constituents in Case 2*

	Date, 1939	Volume, Cc.	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.	Total Base, mEq.	Ammonia, mEq.	Chloride, mEq.	Titratable Acid, mEq.	Phosphate, Gm.	Total Nitrogen, Gm.	p_H	Body Weight, Kg.
Period 1	May 11-12	1,730	210.2	56.0	14.3	333.4	31.5	187.6	19.6	1.19	13.4	7.0	50.7
	12-13	1,660	214.8	63.0	16.3	333.4	29.9	196.2	13.4	1.23	12.4	7.2	50.5
	13-14	1,430	192.5	45.2	14.4	303.4	28.1	171.6	11.6	1.02	11.7	7.1	50.3
	14-15	1,720	193.5	54.4	15.3	314.8	32.9	181.4	13.8	1.01	13.0	7.2	50.2
Period 2	May 19-20	1,760	115.5	50.0	14.4	251.0	46.8	139.6	16.2	0.66	10.5	6.7	50.6
	20-21	1,440	114.8	51.2	17.8	225.0	37.0	120.4	12.6	0.76	11.0	6.8	50.2
	21-22	1,740	85.0	54.0	12.8	205.0	40.2	99.8	16.2	0.88	11.4	6.8	50.2
	22-23	1,510	73.4	61.2	8.8	188.2	24.0	84.2	12.0	0.73	9.3	6.8	50.6

TABLE 7.—*Summary of Data on Metabolic Balance in Case 2*

	Period 1 (Azosulfamide)				Period 2 (Phenobarbital)			
		Output				Output		
Constituents	Intake	Urine	Stool	Daily Balance	Intake	Urine	Stool	Daily Balance
Sodium, mEq.....	787	811	47.6	—17.9	461	389	11.3	+16.2
Potassium, mEq.....	365	219	90.8	+14.1	376	216	47.8	+28.0
Calcium, mEq.....	218	61	139.5	+4.5	216	54	163.2	—0.3
Chloride, mEq.....	391	736	5.3	—87.2	391	444	5.9	—14.7
Phosphate, Gm.....	5.73	4.45	1.28	—0.01	6.08	3.03	1.96	+0.27
Nitrogen, Gm.....	53.7	50.5	6.4	+0.07	54.6	42.2	4.6	+1.9

tion of sodium and chloride was diminished as compared with that in the preceding period. The p_H of the urine was decreased (table 6). There were positive daily balances of sodium of 16.2 milliequivalents, of potassium of 28 milliequivalents, of phosphate of 0.27 Gm. and of nitrogen of 1.9 Gm. (table 7).

COMMENT

The following questions are pertinent to these data: 1. What changes in the acid-base equilibrium of the body are induced by azosulfamide? 2. What mechanisms operate in these changes? 3. What chemical changes are related to the anticonvulsant effect of azosulfamide? 4. What is the mechanism of the anticonvulsant effect? 5. Does this study clarify the etiologic factors or the pathogenesis of epilepsy? It should be mentioned that the small number of cases and the short duration of these studies of such a chronic and variable disorder as epilepsy do not allow the formation of any conclusions universally applicable to epilepsy.

There were several constant observations, which included a decrease in the carbon dioxide content and the carbon dioxide tension of the serum, an increase in the concentration of chloride in the blood and loss of chloride in the urine. There was a negative daily chloride balance. These results are similar to those of other studies made during administration of sulfanilamide [25] and of azosulfamide.[1b]

The mechanism of these changes is not entirely clear. A decreased absorption of bicarbonate [26] by the renal tubules, leading to a lowered carbon dioxide content of the serum, and eventually to a related rise in serum chlorides, has been advanced as the primary change. The decrease in carbon dioxide tension may be due to the inhibiting action of azosulfamide on carbonic anhydrase.[27] The loss of chlorides in the urine accompanies the increased excretion of sodium. This was evident in case 2, in which azosulfamide medication had been employed for some time, but was obscured in the balance study in case 1, in which the effect of the drug lasted well into the control period, period 3.

In general, conditions which are accompanied by a decrease in the carbon dioxide content of the serum,[28] such as hyperventilation, are detrimental to patients with epilepsy, while, conversely, an increase in the carbon dioxide of the serum is helpful; i. e., petit mal attacks decrease [29] and abnormal electroencephalographic records improve.[30] Azosulfamide is a drug that shows anticonvulsant action in the presence of a low carbon dioxide content and a low carbon dioxide tension of the serum.

This may not be a discrepancy, as in this instance the carbon dioxide content of the blood may not reflect accurately the carbon dioxide content of the tissues. It has been demonstrated that carbonic anhydrase, the enzyme which plays a great part in controlling the release of carbon dioxide, is poisoned by sulfanilamide.[31] Therefore there arises the possibility, which thus far is speculation, of a low carbon dioxide content of the serum with a high content of the tissues. This could occur if the tissues were not able to get rid of their carbon dioxide efficiently. The levels of sulfanilamide in the blood in this study (tables 1 and 5) approximated the levels at which the poisoning effect of sulfanilamide on carbonic anhydrase begins to appear.[31a]

Diuresis following administration of azosulfamide has been reported [25a] but was not observed in our patients.

There is a decrease in p_H, but longer studies in these and in other cases [1b] have shown that the p_H does not remain at a low level permanently but fluctuates in the

25. (*a*) Beckman, W. W.; Rossmeisl, B. C.; Pettingill, R. B., and Bauer, W.: A Study of the Effects of Sulfanilamide on Acid-Base Metabolism, J. Clin. Investigation **19**:635, 1940. (*b*) Strauss, M. B., and Southworth, H.: Urinary Changes Due to Sulfanilamide Administration, Bull. Johns Hopkins Hosp. **63**:41, 1938.

26. McChesney, E. W.; Sprague, K. D., and Marshall, I. H.: The Effect of Sulfanilamide on Acid-Base Balance, J. Lab. & Clin. Med. **26**:1154, 1941; correction, ibid. **26**:1394, 1941. Beckmann and associates.[25a]

27. (*a*) Keilin, D., and Mann, T.: Activity of Carbonic Anhydrase Within Red Blood Corpuscles, Nature, London **148**:493, 1941. (*b*) Wood, W. B., and Favour, C. B.: The Relation of Sulfanilamide "Acidosis" to the Specific Inhibition of Carbonic Anhydrase, J. Clin. Investigation **20**:433, 1941.

28. Lennox, W. G., and Cobb, S.: Epilepsy, Harvard Medicine Monographs, Baltimore, Williams & Wilkins Company, 1928, vol. 14.

29. Lennox, W. G.: The Effect of Epileptic Seizures on Varying the Composition of Respired Air, J. Clin. Investigation **6**:23, 1925.

30. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variation in the CO_2 Content in the Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223 (Feb.) 1940.

31. (*a*) Roughton, F. J. W.; Dill, D. B.; Darling, R. C.; Graybiel, A.; Knehr, C. A., and Talbott, J. H.: Some Effects of Sulfanilamide on Man at Rest and During Exercise, Am. J. Physiol. **135**:77, 1941. (*b*) Keilin and Mann.[27a] (*c*) Wood and Favour.[27b]

normal range. The p_H of the urine was higher in both periods of azosulfamide medication than in the control periods or in the periods of administration of phenobarbital.

Of greatest interest was the positive potassium balance observed in both cases during or shortly after periods of administration of azosulfamide. In case 2 this was evident in the period of azosulfamide medication. In case 1 the positive potassium balance did not reach its height until the following control period. It can be noted in this case (table 2; chart 2) that as long as the potassium level was low in the urine there were no seizures. A rise in urinary potassium on the fourth day

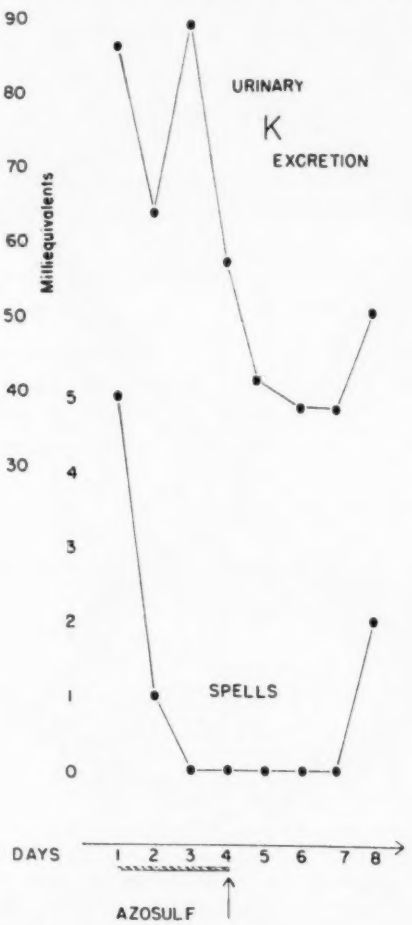

Chart 2.—Decrease in urinary excretion of potassium (*K*) with decrease in number of spells accompanying administration of azosulfamide (*azosulf.*). Azosulfamide was discontinued at the point indicated by the arrow, and the spells returned after three days, coincident with the increase in excretion of potassium.

was accompanied by a return of seizures. This coincides with similar observations on an epileptic patient by McQuarrie,[32] who showed in a metabolic study that the appearance of convulsions was preceded by heightened excretion of potassium in the urine and by a rise in the potassium-sodium ratio of urinary excretion. The

32. McQuarrie, I.; Manchester, R. C., and Husted, C.: Study of the Water and Mineral Balances in Epileptic Children: I. Effects of Diuresis, Catharsis, Phenobarbital Therapy and Water Storage, Am. J. Dis. Child. **43**:1519 (June) 1932.

latter change was also noted by us with administration of azosulfamide. In this study there was a positive potassium balance with phenobarbital. This corresponds to a previous observation by McQuarrie.[32] If storage of potassium coincides with or causes an anticonvulsant effect, the mechanism is unknown. It is known that potassium plays a role in nerve function, but its exact action is not clear.[33]

Ammonium chloride produced the same degree of decrease in the p_H initially. A positive chloride balance occurred simultaneouly. The decrease in carbon dioxide content and carbon dioxide tension of serum was comparable to that produced by azosulfamide, but there were no anticonvulsant effects. From the results in this period, it was concluded that the effect of azosulfamide is not simply a result of

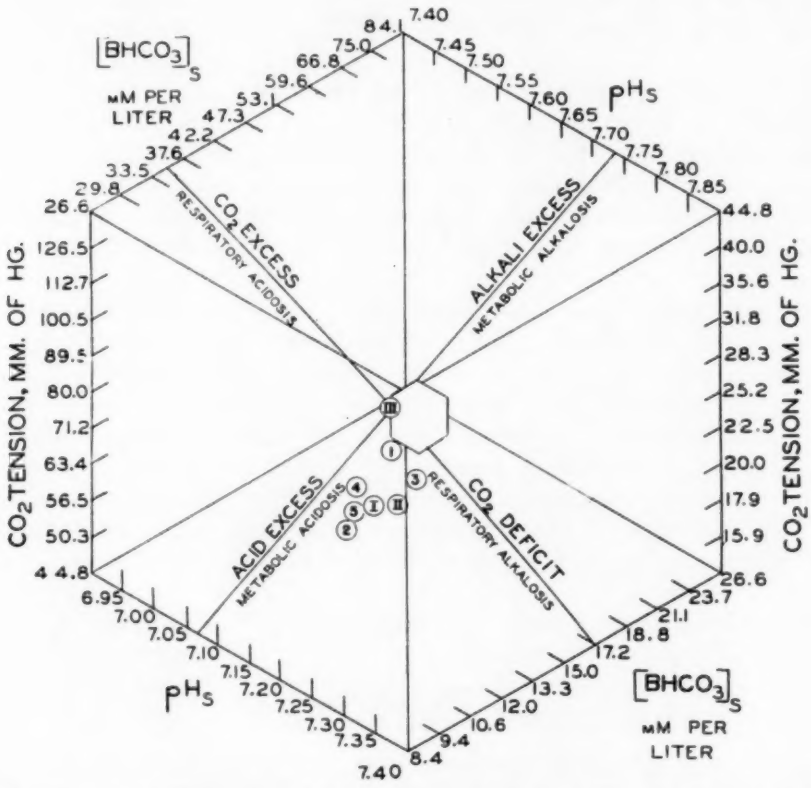

Chart 3.—Case 1 (Arabic numerals): *1*, control period, with normal values; *2*, period of azosulfamide therapy, with decrease in carbon dioxide tension, bicarbonate content and p_H of the serum; *3*, control period, with swing back to slight respiratory alkalosis; *4* and *5*, effects of ammonium chloride, paralleling those of azosulfamide (*2*).

Case 2 (Roman numerals): *I* and *II* indicate effects of azosulfamide, with a slighter degree of metabolic acidosis than that indicated in *2*. *III* denotes the period of administration of phenobarbital, with values falling within the normal range.

Note: In this nomogram, p_{Hs} (p_H of serum), $BHCO_3$ (bicarbonate of serum), expressed in millimols per liter, and carbon dioxide tension (pressure of carbon dioxide, expressed in millimeters of mercury) are charted. The circles with numerals indicate the value for each.

the decreased carbon dioxide content of the serum or of the p_H, but that some other factor must play a role.

33. Fenn, W. O.: Role of Potassium in Physiological Processes, Physiol. Rev. **20**:377, 1940.

The well known anticonvulsant action of phenobarbital was demonstrated to take place with no concomitant change in the acid-base balance of the serum. It can be seen, thus (chart 3), that azosulfamide produces acidosis and an anticonvulsant effect; ammonium chloride, acidosis and no anticonvulsant effect, and phenobarbital, an anticonvulsant effect and no acidosis. This suggests that "acidosis" is not necessarily the crucial factor in anticonvulsant action.

CONCLUSIONS

1. Administration of azosulfamide is accompanied by a decrease in the carbon dioxide content and the carbon dioxide tension of the serum.

2. The decreased carbon dioxide content and the lowered carbon dioxide tension of serum accompany the anticonvulsant effect.

3. The anticonvulsant effects of both azosulfamide and phenobarbital coincide with a positive potassium balance.

4. Ammonium chloride produces the same degree of "acidosis" as does azosulfamide, without alteration of potassium exchange, and does not have an anticonvulsant effect.

5. Phenobarbital produces no "acidosis," but a positive potassium balance, and has an anticonvulsant effect.

Massachusetts General Hospital.
275 West Federal Street, Youngstown, Ohio.
Massachusetts General Hospital.
24 Oldham Road, Newton, Mass.

MINERAL CONSTITUENTS IN BLOOD SERUM AND CELLS OF SCHIZOPHRENIC PATIENTS

DISTRIBUTION OF SODIUM, POTASSIUM, CALCIUM, MAGNESIUM, INORGANIC PHOSPHORUS AND CHLORIDE

SOLOMON KATZENELBOGEN, M.D.
AND
ENSIGN REBECCA SNYDER, U.S.N.R.
WASHINGTON, D. C.

This study was undertaken with the object of finding out the content of sodium, potassium, calcium, magnesium, inorganic phosphorus and chloride in the blood cells and the serum of schizophrenic patients. Until recent years studies of minerals in the blood of patients with mental disorders have been concerned exclusively with either the serum or the whole blood. In 1938 Chatagnon [1] reported on a study of the chloride content of the cells in 7 schizophrenic patients. This was followed by another comprehensive investigation of the same problem by Gross, Gross and Wortis, in 1940.[2] To our knowledge there are in the literature no further studies on the anion and cation concentrations in the blood cells of schizophrenic patients.

EXPERIMENTAL PROCEDURE

Blood was obtained from an antecubital vein of 9 schizophrenic patients before they had had breakfast. The blood was collected over mercury and defibrinated according to the technic of Eisenman.[3] The defibrinated blood was then centrifuged under oil, and cells and serum were separately analyzed for sodium, potassium, calcium, magnesium, inorganic phosphorus and chloride by methods described in a previous publication.[4] The specimens were carefully examined for traces of hemolysis and were discarded if such were found.

RESULTS

Our results are compiled in the accompanying table. With few exceptions, the analytic data fell within the ranges obtained for our normal group.[4] In 5 patients (cases 2, 12, 14, 21 and 26) the values for serum potassium exceeded the upper limit for our normal group. However, our control group was comparatively small, and other investigators have reported for normal subjects values for serum potassium higher than any obtained for our schizophrenic patients or for normal subjects (Snyder and Katzenelbogen,[4] table II). In only 1 subject (case 16) was the value for inorganic phosphorus of blood cells above the maximum value for our normal group.[4] As was mentioned before, the cell chlorides in schizophrenic

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1. Chatagnon, C.: Le chlore sanguin chez les schizophrènes, Compt. rend. Soc. de biol. **128**:868-870, 1938.

2. Gross, M.; Gross, G. M., and Wortis, S. B.: Biochemical Studies in Schizophrenia: The Chlorides in Blood Plasma and Red Blood Cells, Psychiatric Quart. **14**:834-849, 1940.

3. Eisenman, A. J.: Method for Anaerobic Defibrination of Blood, J. Biol. Chem. **71**: 607-609, 1927.

4. Snyder, R., and Katzenelbogen, S.: The Distribution of Sodium, Potassium, Calcium, Magnesium, Inorganic Phosphorus, and Chloride Between the Blood Serum and Cells of Normal Individuals, J. Biol. Chem. **143**:223-226, 1942.

Case No.	Age, Yr.	Type of Schizophrenia	Source*	Sodium		Potassium		Calcium		Magnesium		Inorganic Phosphorus		Chloride	
				Mg. per 100 Cc.	mEq.	Mg. per 100 Cc.	mEq.	Mg. per 100 Cc.	mEq.	Mg. per 100 Cc.	mEq.	Mg. per 100 Cc.	mEq.	Mg. per 100 Cc.	mEq.
1	24	Catatonic	S	330.4	143.7	24.2	6.2	10.7	5.3	2.8	2.3	3.4	2.2	367.1	103.5
			C	35.3	15.4	386.1	98.8	1.2	0.6	3.6	3.0	3.7	2.4	207.3	58.5
2	21	Catatonic	S	295.4	128.4	25.7	6.6	10.0	5.0	3.2	2.6	3.4	2.2	354.3	99.9
			C	33.8	14.7	315.9	80 8	0	0	4.7	3.9	1.4	0.9	185.3	52.3
3	21	Catatonic	S	310.7	135.1	.....	....	8.7	4.3	3.5	2.9	3.9	2.5	362.8	102.6
			C	35.4	15.4	350.0	89 8	0.4	0.2	4.5	3.7	2.5	1.6	192.4	54.4
4	19	Catatonic	S	325.0	141.3	19.1	4.9	10.1	5.0	2.5	2.1	3.1	2.0	353.6	99.7
			C	28.7	12.5	339.3	86 8	0	0	5.0	4.1	Tr.	Tr.	216.6	61.1
5	20	Catatonic	S	328.6	142.9	22.6	5.8	10.0	5.0	...	...	3.9	2.5	352.9	99.5
			C	35.1	15.3	302.2	77.3	0	0	4.9	4.0	1.2	0.8	214.4	60.5
6	21	Catatonic	S	308.6	134.2	18.7	4.8	9.3	4.6	2.6	2.1	4.1	2.6	360.7	101.7
			C	30.5	13.3	347.1	88.8	0	0	5.0	4.1	2.8	1.8	210.2	59.3
7	21	Catatonic	S	311.0	135.2	20.3	5.2	9.5	4.7	2.2	1.8	3.2	2.1	366.4	103.3
			C	46.0	20.0	337.3	86.3	0	0	4.4	3.6	1.7	1.1	175.4	49.5
8	25	Catatonic	S	315.4	137.1	16.0	4.1	9.5	4.7	2.4	2.0	4.1	2.6	364.2	102.7
			C	26.5	11.5	325.6	83.5	0	0	2.7	2.2	1.4	0.9	207.7	58.6
9	26	Catatonic	S	304.4	132.3	16.8	4.3	9.0	4.5	2.4	2.0	3.4	2.2	376.3	106.1
			C	39.6	17.2	304.2	78.0	0	0	4.2	3.4	0.7	0.4	211.6	59.7
10	21	Catatonic	S	314.5	136.8	22.2	5.7	....	...	4.5	3.7	3.3	2.1	352.9	99.8
			C	25.7	11.2	338.3	86.7	0.5	0.2	5.3	4.4	0.3	0.2	206.6	58 4
11	26	Catatonic	S	312.9	136.1	17.4	4.5	10.0	5.0	2.2	1.8	2.8	1.8	371.3	105.0
			C	30.6	13.3	311.0	79.8	0.8	0.4	4.2	3.4	1.9	1.2		
12	36	Catatonic	S	299.6	130.3	26.5	6.8	9.5	4.7	2.9	2.4	4.0	2.6	348.6	98.3
			C	14.0	6.1	351.4	90.1	0	0	4.6	3.8	5.4	3.5	195.2	55.1
13	37	Catatonic	S	.....	....	.....	....	9.8	4.9	2.7	2.2	3.0	1.9	355.4	100.2
			C	64.3	28.0	339.3	86 8	2.0	1.0	3.3	2.7	Tr.	Tr.	193.1	54.5
14	39	Catatonic	S	313.3	136.2	26.5	6.8	9.3	4.6	2.3	1.9	3.3	2.1	399.7	112.7
			C	0	0	376.0	96.4	0	0	4.2	3.4	2.9	1.9	251.8	71.0
15	18	Hebephrenic	S	327.1	142.2	17.2	4.4	9.7	4.8	...	...	3.6	2.3	362.1	102.1
			C	26.8	11.6	327.6	83.8	0	0	4.3	3.5	4.2	2.7	200.2	56.5
16	21	Hebephrenic	S	312.4	135.8	18.3	4.7	8.5	4.2	2.4	2.0	4.0	2.6	358.6	101.4
			C	34.9	15.2	352.0	90.3	0	0	2.6	2.1	10.2	6.6	181.8	51.4
17	29	Hebephrenic	S	314.8	136.9	17.2	4.4	10.4	5.2	2.7	2.2	5.8	3.7	360.7	101.7
			C	5.4	2.3	327.6	84 0	0	0	2.2	1.9	1.0	0.6	210.9	59.5
18	30	Hebephrenic	S	328.9	143.0	19.9	5 1	9.2	4.6	2.8	2.3	3.7	2.4	350.0	98.7
			C	16.4	7.1	351.4	90 1	1.8	0.9	4.7	3.9	5.0	3.2	192.1	54.2
19	32	Hebephrenic	S	337.9	146.9	22.6	5.8	10.6	5.3	3.0	2.5	4.0	2.6	345.8	97.5
			C	36.6	15.9	347.1	88.8	1.1	0.5	4.4	3.6	3.5	2.2		
20	37	Paranoid	S	306.5	133.3	21.8	5.6	8.1	4.0	2.5	2.0	3.5	2.2	369.2	104.4
			C	24.5	10.6	335.4	86.0	0.7	0.3	5.7	4.7	1.8	1.2	193.1	54.6
21	47	Paranoid	S	328.8	143.0	25.0	6.4	10.0	5.0	2.5	2.1	3.8	2.4	374.9	105.7
			C	27.2	11.8	354.9	90.8	1.2	0.6	4.4	3.7	3.3	2.1	199.5	56.3
22	29	Mixed	S	301.4	131.0	23.8	6.1	8.8	4.4	2.3	1.9	3.8	2.4	364.9	103.2
			C	14.2	6.2	351.0	90.0	0.4	0.2	...	...	2.0	1.3	192.4	54.4
23	29	Mixed	S	330.4	143.7	19.5	5.0	10.7	5.3	2.8	2.3	4.4	2.8	357.0	100.7
			C	29.0	12.6	315.9	80.9	0	0	4.6	3.8	...	...	219.1	61.8
24	22	Mixed	S	332.6	144.6	21.5	5.5	9.8	4.9	2.9	2.4	3.4	2.2	357.8	100.9
			C	41.9	18.2	347.1	88 8	0	0	4.7	3.9	2.2	1.4	186.7	52.6
25	19	Mixed	S	310.5	135.0	19.1	4.9	10.0	5.0	2.9	2.4	3.0	1.9	402.6	113.5
			C	0.2	0.1	329.2	84 4	0	0	3.4	2.8	1.7	1.1	169.0	47.7
26	26	Undetermined	S	327.6	142.5	25.4	6.5	....	...	1.5	1.2	3.6	2.3	363.5	102.8
			C	36.2	15.7	331.5	85.0	....	...	2.1	1.7	1.5	1.0	203.1	57.4
27	22	Undetermined	S	297.0	129.1	23.4	6.0	9.7	4.8	2.1	1.7	3.5	2.2	352.1	99.6
			C	23.6	10.3	367.6	94 3	0	0	3.5	2.9	0.7	0.4	205.7	58.2
28	19	Undetermined	S	313.5	139.5	19.2	4.9	9.6	4.8	2.5	2.0	3.8	2.4	353.6	100.0
			C	27.9	12.1	341.9	87.7	0	0	4.4	3.6	2.5	1.6	196.4	55.6
29	19	Undetermined	S	312.2	135.8	18.7	4.8	10.3	5.1	1.9	1.6	4.0	2.6	360.0	101.8
			C	43.5	18.9	360.8	92 5	0.7	0.3	3.4	2.8	1.7	1.1	208.0	58.8
Ranges.....			S	295.4-337.9	128.4-146.9	16 0-26.5	4 1-6 8	8.1-10.7	4.0-5.3	1.5-4.5	1.2-3.7	2.8-5.8	1.8-3.7	345.8-402.6	97.5-113.5
			C	0.0-64.3	0.0-28.0	302.2-386.1	77.3-98 8	0.0-2.0	0.0-1.0	2.1-5.7	1.7-4.7	Tr.-10.3	Tr.-6.6	169.0-251.8†	47.7-71.0†

* S indicates serum, and C, cells.

†Exclusive of the range for 1 case: 169.0 to 219.1 and 47.7 to 61.8.

patients have been reported on in two previous studies. Chatagnon [1] found normal values in 7 patients, whereas Gross, Gross and Wortis,[2] from a study on 38 schizophrenic patients, concluded that there was an increase in the chloride content of the red blood cells, particularly notable in the catatonic patients. The present study shows an abnormally high value for cell chlorides in only 1 of our 29 patients (case 14).

These conflicting data may possibly be explained by differences in the emotional states of the patients at the time the specimens of blood were taken. Fluctuations in serum potassium and serum calcium associated with changes in the phase of illness have been reported by Minker-Bogdanova, Povorinskaya and Povorinsky [5]; Walther and Gordonoff,[6] and Gullotta.[7] Our patients, at least during the making of the venous punctures, showed no outward signs of unusual emotional disturbance.

SUMMARY

The blood cells and serum of 29 schizophrenic patients were analyzed for sodium, potassium, calcium, magnesium, inorganic phosphorus and chloride. As compared with the results we previously obtained with 12 normal subjects,[4] the present study showed slight elevation of serum potassium in 5 patients and of the chloride and inorganic phosphorus contents of the cells in 1 case each. The other mineral values were within the ranges of our normal group. The differences between some of our values and those of other investigators may possibly be attributed to the differences in the emotional state of the patients at the time the specimens of blood were obtained.

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MEASUREMENT OF INTELLECTUAL FUNCTIONS IN THE ACUTE STAGE OF HEAD INJURY

JURGEN RUESCH, M.D.
AND
BURNESS E. MOORE, M.D.
BOSTON

The state of consciousness immediately following injury to the head is the subject of this study.[1] Although measurement of mental functioning in the early stages of injury would be an aid to correct diagnosis and prognosis, to our knowledge no similar investigation of the intellectual functions has been made until convalescence. This is true because surgical complications and damage to vital centers usually monopolize attention immediately after head trauma. It seemed of interest, therefore, to determine the degree of incapacity within the first twenty-four hours and to observe the subsequent course of the mental disability. The status of consciousness was measured by the ability of the subject to submit to psychologic testing, and the results of these examinations were compared with the type and severity of the injury.

CASE MATERIAL

For investigation of the psychometric performance in the first twenty-four hours after injury, patients were studied who had been brought to the Boston City Hospital within approximately two hours after the accident. All patients admitted on alternate days and nights were accepted in order that an unselected sample of persons with head injuries might be obtained. In this way a series of 190 patients was secured. Of these, 80 per cent were males and 20 per cent females. Their ages ranged from 2 to 84 years, with a mean of 39 years. Fifteen per cent of the subjects were children under the age of 13 years. Although all racial groups were represented, the majority were of Irish origin.

For the study of improvement in the succeeding days, the selection of patients was necessarily confined to those with a minimal stay in the hospital of four days. Eighty-five such patients were repeatedly examined during hospitalization. Sixty-six per cent were males and 34 per cent females. The ages ranged from 11 to 67 years, with a mean age of 35 years. Out of both groups, 70 patients submitted to reexamination after discharge. The mean intelligence quotient was 94.5, with a standard deviation of ± 13.1, an indication that the sample of the population studied belonged to the group of low average intelligence.

PROCEDURE

The tests were selected to meet conditions imposed by the hospital environment. Injured patients are usually kept flat in bed, and methods of examination must be independent of body position. It was desired to follow the patients over a period of years, so that their active cooperation had to be assured, although the attitude of general hospital patients toward psychologic testing is often reserved, or even unfriendly. Hence, the procedures which might imply suspicion of low intelligence or doubt of sanity were minimized, and, in order to win the person's confidence, each session was preceded by an explanation of the need to test "mental speed." Preoccupation with the accident, serious and painful injuries and fatigue are often factors limiting the time of examination, and methods had to be selected to cover the widest possible range of mental functions within an allotted period of fifteen minutes. To meet these conditions five simple tests were used, and they are described in the next section.

From the Neurological Unit of the Boston City Hospital and the Department of Neurology of the Harvard Medical School.

1. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard Medical School. This study is part of an investigation of the sequelae of head injuries being conducted at the Neurological Unit of the Boston City Hospital.

Examination was attempted as soon as a subject became responsive. Failure to do a given task within the first twenty-four hours was considered evidence of complete incapacity. Since the study dealt with a population of heterogeneous intellectual background, comparison of results of the tests with norms is of secondary importance only. Emphasis is placed on the ability of the patient to submit to testing within the first twenty-four hours and the measured improvement within the next few days. In subsequent paragraphs group performances will be discussed. In conformity with customary statistical requirements,[2] the difference of two means is considered significant when the difference of the means divided by the standard error of the difference equals or exceeds 3.

TESTS

The 100 —7 Test.—The subject is instructed to "take 7 away from 100, then to take 7 from the result obtained, and so on." The performance is timed if done in less than two minutes; a period of over two minutes is recorded as one hundred and twenty seconds. The errors are counted by considering each subtraction as a single operation. More than 6 errors constitutes failure. According to Hayman,[3] a subject with a mental age of 15 years is able to perform the test with less than 1 error. It is safe to assume that any one who attended high school should be able to perform the test adequately and that any one who has completed at least seven years of grammar school should be able to pass the test, although with several errors. The mental functions examined are the abilities to calculate, to retain, to recall and to keep up a sustained effort (attention). The test is valuable as an indicator of intellectual efficiency and of mental speed and is well adapted to repeated examinations. Since the starting point can be set at 102, 101, 100, 99, 98, and so on, the learning factor may be neglected.

Auditory Span for Digits Repeated Forward and Backward.—The subject is instructed to repeat the digits given him by the examiner. The digits are spoken at the rate of 1 per second, and a series of 4 is usually given first. The score is the highest number of digits repeated without error on either of two trials. For the repetition of digits backward, several examples are given, until the patient understands the task. The examiner starts with 3 digits, and the score is the highest number of digits reversed without error on either of two trials. The norm for adults is 6 to 7 digits repeated forward and 2 less repeated backward. If these two values are added, the total should be 11 to 12 digits (Wells and Ruesch[4]; Terman[5]; Wechsler[6]). The chief functions tested are ability to concentrate (attention) and rote memory (retention).

Visual Span for Objects.—The subject is shown a picture (Wells-Ruesch[4] manual) with 10 familiar objects. The examiner, pointing to each object one by one, asks: "What is this?" Then the picture is turned over, and the subject is asked to repeat the names of the objects seen. Six or more items remembered can be considered as the norm (table). The test measures visual recognition, recall and habitual attention. Six different sets of pictures are provided in order to allow repeated examinations.

Pictorial Similarities.—Three pictures, each with 10 similar objects (Wells-Ruesch Manual[4]), such as tools, fruits, dishes and stationery, are shown to the subject. He is then asked: "What are all these things?" If he starts to enumerate the items, he is asked to give one name which expresses the similarity of all the objects. A normal adult should easily find all the correct names. The maximal score is 3. Different sets of pictures allow repeated examinations. Abstraction is the primary function involved.

Pictorial Absurdities.—Two sets of pictures, containing 5 absurd items each, are used (Wells-Ruesch manual[4]). The subject is shown one picture at each session and is asked: "What is wrong with this picture?" For each absurdity recognized 1 point is assigned. The maximal score is 5. Normal adults of average intelligence should recognize 4 to 5 absurdities. The functions tested are visual recognition, reasoning and judgment. The test does not require formal education; rather, it calls for practical experience in life.

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RESULTS OF PSYCHOMETRIC TESTS GIVEN WITHIN TWENTY-FOUR HOURS AFTER INJURY TO THE HEAD

Of 190 patients examined within the first twenty-four hours after the accident, 120 (63 per cent) could be tested by psychometric methods, whereas the condition of 70 others (36 per cent) did not allow this approach. In figure 1 the 190 subjects have been distributed according to their diagnostic aspects. The blank columns show the percentage of patients who could be tested, while the filled-in columns represent the percentage of patients who could not be subjected to psychologic examination. The highest incidence of incapacity occurred in the patients with intracranial hematomas (75 per cent), although the number represented was too small for one to draw conclusions. This group is followed by the groups of patients with fractures of the skull (58 per cent), bloody spinal fluid (43 per cent), alcoholism (36 per cent) and simple loss of consciousness (32 per cent).

Consideration of the factors preventing examination of the 70 patients who could not be tested (filled-in columns, figure 1) reveals that in 27 per cent the cause did not arise from injury to the head. In only 9 per cent of all the 190 subjects did reasons directly related to head injury prevent examination; coma and semicoma thus accounted for 5 per cent, and delirium and confusion, for 4 per cent. Pro-

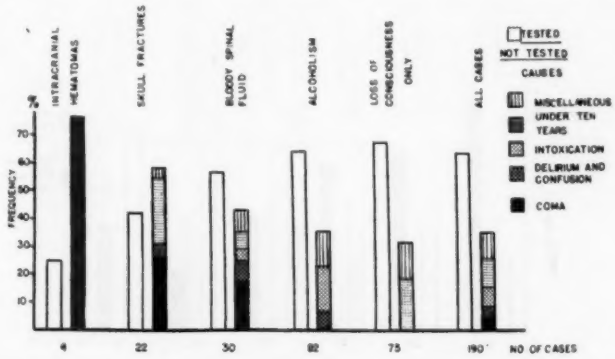

Fig. 1.—Relation of diagnostic criteria to ability of patients to cooperate in tests within the first twenty-four hours after injury to the head.

Results of a Series of Tests Given an Unselected Group of Patients with Head Injuries Within Twenty-Four Hours After Admission *

	Patients with Fracture of Skull (9)		Patients with Bloody Spinal Fluid (18)		Patients with Acute or Chronic Alcoholism (52)		Patients with Loss of Consciousness Only (51)		All Patients (120)	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
100—7 test: Complete failure....	1	11	12	66	25	48	14	27	47	39
Above time limit....	0	0	11	60	4	8	7	14	16	13
	M.	S. D.	M.	S. D.	M.	S. D.	M.	S. D.	M.	S. D.
Errors.....	1.7	1.2	1.0	1.2	1.7	1.5	2.3	1.8	1.9	1.8
Time.....	54 sec.	29 sec.	61 sec.	12 sec.	67 sec.	28 sec.	62 sec.	27 sec.	61 sec.	25 sec.
Digit span—Total.....	8.7	2.7	7.9	2.6	8.1	3.1	9.2	2.4	9.1	2.1
Forward.....	5.5	1.0	4.8	1.5	5.0	1.9	5.7	1.0	5.6	1.0
Backward.....	3.2	1.8	3.1	1.2	3.1	1.0	4.1	1.7	3.6	1.2
Visual span for objects.....	5.7	1.0	5.8	2.5	5.6	2.4	6.6	1.4	6.4	1.4
Pictorial abstractions.....	3.0	0.0	2.8	1.9	2.4	1.0	2.9	0.5	2.8	0.5
Pictorial absurdities.....	4.0	0.8	2.2	1.1	2.8	1.4	4.0	1.6	3.5	1.6
Age.....	22 yr.	14 yr.	42 yr.	17 yr.	45 yr.	15 yr.	30 yr.	21 yr.	37 yr.	20 yr.

* In this table, M. indicates the group mean, and S. D., the corresponding standard deviation.

longed coma was most frequent in the patients with hematoma (75 per cent), fractures of the skull (27 per cent) and bloody spinal fluid (18 per cent); the incidence for alcoholic patients was only 1 per cent. In no instance did a patient with simple loss of consciousness exhibit coma, delirium or confusion which lasted longer than twelve hours, so that all such subjects could be tested within the first day.

In analysis of the results with testable patients, the table reveals that some subjects who were able to repeat digits, to memorize objects or to consider absurd pictures were still unable to do the 100 — 7 test. Complete failure in serial subtraction occurred most frequently in patients with bloody spinal fluid (66 per cent) and in alcoholic patients (48 per cent). Only 27 per cent of patients with simple loss of consciousness failed. It is striking that this order is the same as that exhibited for total incapacity to perform on all tests (fig. 1). The values for the measured performances have been presented in terms of group means (M), with corresponding standard deviations (S. D.) (table). Comparison of the mean values for the various diagnostic groups does not show any statistically significant differences.

The level of performance, however, was rather low for all groups. A total digit span of about 9 was about 1 sigma below the norm which has been established for

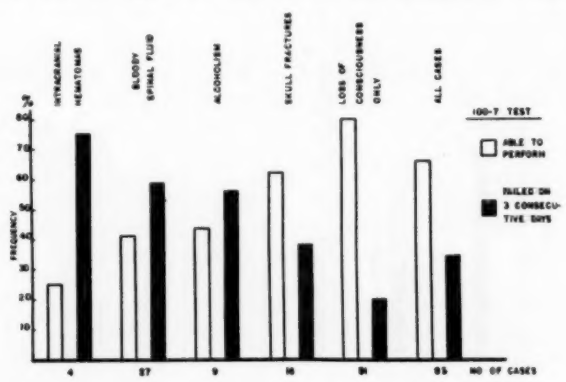

Fig. 2.—Diagnostic distribution of 85 patients examined in three consecutive days after injury to the head.

an average population.[6] The number of errors and the high incidence of failures in serial subtraction tests were also striking. Most values were below the figure which corresponds to the average intelligence quotient of 94 found in a sample of the population studied.[7]

RESULTS OF SERIAL SUBTRACTION TESTS ON THREE SUCCESSIVE DAYS AFTER INJURY

The preceding observations are suggestive of slight, but definite, disturbance of intellectual functioning in the first twenty-four hours after the accident. It seemed of interest to inquire whether this suspected defect could be substantiated by later improvement in test scores. Investigation of the duration of the impairment was attempted in order to learn whether recovery begins within the first few days or appears only later. The serial subtraction test, being the most sensitive,[7] was selected for this purpose.

The 100 — 7 test was given to 85 patients at daily intervals for the first three days after injury. Figure 2 demonstrates the percentages of patients who were

7. Ruesch, J.: Intellectual Impairment in Head Injuries, Am. J. Psychiat., to be published.

able (66 per cent) and the percentage who were unable (34 per cent) to perform at any time during this period. Comparison of failures in the diagnostic subgroups in the first twenty-four hours (fig. 1) with those in the first seventy-two hours (fig. 2) reveals the same sequence, except for the patients with fractures of the skull. This indicates that the patients with fracture had a more rapid intellectual recovery than the other groups. The data on 56 patients who were able to execute psychometric tasks are shown in figure 3. The values for the first four days and those for follow-up tests (one to three months after the accident) were charted. The time needed to do serial subtractions did not improve remarkably within the first four days, since the differences of the means were statistically insignificant. Valid differences existed, however, between any of the values for the first four days and the subsequent follow-up figure. This fact demonstrates that performance time showed the greatest improvement after the fourth postinjury day.

Comparison of the mean number of errors made on the four successive days does not reveal any statistically valid differences. Significant, however, is the difference between the follow-up figure and the means for the first, second and third days. The trend of improvement in accuracy is more obvious and appears earlier than is true for time. In the present series of subjects a valid difference between the two

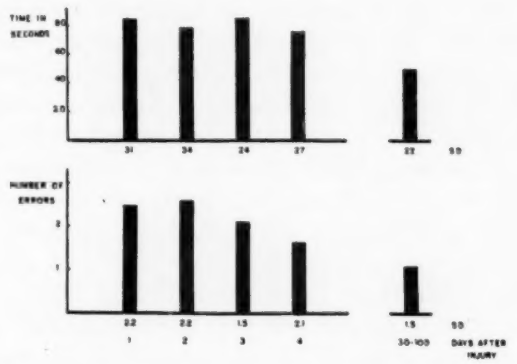

Fig. 3.—Mean values for 56 patients in the serial subtraction test during the first four days after head injury.

means is represented by a figure which for time should exceed about twenty seconds and for accuracy about 1 error.

COMMENT

The results of psychometric examinations of 190 patients with head injuries, studied within twenty-four hours of the accident, are reported. Serial subtraction tests were repeated with 85 patients on four consecutive days after admission to the hospital.

Special consideration was given to the patients unable to submit to psychologic testing. Complete intellectual impairment for the first twenty-four hours was found in decreasing order of frequency in patients with intracranial hematoma, fracture of the skull, bloody spinal fluid, alcoholism and simple loss of consciousness. Inability to perform, if related to head injury, was caused by coma or confusion. It follows that the disturbance of consciousness after injury to the head can be measured by the ability to submit to testing and is an expression of the severity of the damage to the brain.

For subjects able to perform, the results of the procedures indicate that serial subtraction is the more sensitive test. While some of the patients were able to repeat digits or to interpret pictorial absurdities, they were often still unable to

perform the 100 — 7 test. Total disability in the first twenty-four hours, failure on serial subtraction alone and inability to do the 100 — 7 test throughout the first three days may be compared. All three types of failure were most frequent in patients with bloody spinal fluid, next most frequent in alcoholic patients and least frequent in those with loss of consciousness only, patients with fracture of the skull excepted. The quick recovery of the patients with skull fracture might indicate that the incapacity immediately following head injury is due less to damage to the central nervous system than to other factors.

Accuracy of performance in the 100 — 7 test shows an earlier trend of improvement than does speed, but improvement in both respects seems to become significant only if intervals of several weeks are considered. Performances on the other tests seem to be much less impaired.

These statistical findings are corroborated by personal observations that the period of complete incapacity is followed by an interval in which simple tasks, such as repetition of digits or naming and recalling of objects, can be done. The next step toward improvement is reached when pictorial absurdities can be interpreted. A level of more normal functioning is attained when serial subtraction can be executed fluently. This period of recovery was very short in all patients with loss of consciousness only, and in our series was protracted for days or weeks only when complications were present. It might be emphasized that the complications are not necessarily the cause of the prolongation of the period of intellectual incapacity, but are collateral evidence of greater severity of the injury.

Though measurement of mental functions can be expressed only in terms of performance, it is of interest to consider the hypothetic mental functions which may be involved. Since serial subtraction proved to be the most sensitive test in our selection, it follows that calculation, retention or the ability to keep up a sustained effort must be damaged after injury to the head. It has been shown elsewhere [7] that retention of digits and objects is not particularly affected, in contrast to the poor performance in interpretation of absurd pictures. The latter is an expression of poor judgment with regard to visual perception. The outstanding defect, therefore, seems to be one in which a sustained effort cannot be maintained, performance time is slowed and judgment is slightly impaired, but often not to an extent sufficient to influence common behavior. It seems advisable to submit all subjects with head injury to such tests, since inspection and ordinary conversation prove to be insufficient means of detecting these intellectual defects. Though failure may occasionally be due to unsatisfactory education, information pertaining to the highest school grade passed may contribute to the accurate assessment of the post-traumatic intellectual condition.

SUMMARY

The status of consciousness immediately following injury to the head was determined in 190 patients by subjecting them to a series of psychologic tests. Complete failure, failure on serial subtraction alone and impaired performance on several tests represent three degrees of intellectual defect.

Patients with severe head injuries leading to intracranial hematoma, fracture of the skull and a bloody spinal fluid have a higher incidence of total intellectual incapacity, of varying duration, than patients with short loss of consciousness only. Prolonged coma, delirium and confusion were much more frequent with the severe lesions and did not occur in patients with simple loss of consciousness.

Examination of 85 patients on three consecutive days by the 100 — 7 test revealed that accuracy of performance improves more during this period than speed. Complete restitution, however, required a period of weeks.

Neurological Unit, Boston City Hospital.

HISTOGENESIS OF THE EARLY LESIONS OF MULTIPLE SCLEROSIS

II. ACUTE MULTIPLE SCLEROSIS

I. MARK SCHEINKER, M.D.
CINCINNATI

There is confusion in the literature in regard to the classification of the acute and chronic forms of multiple sclerosis. In 1885 Babinski,[1] in his thesis on multiple sclerosis, described a "destructive form" of the disease, characterized by extreme rapidity of its course. It was not until 1906 that Marburg [2] described in detail acute multiple sclerosis, which he asserted was a form of true multiple sclerosis characterized by a more rapid course. He emphasized the identity of the two diseases. The confusion became greater after certain authors (Putnam,[3] Pette [4] and others) expressed the view that different forms of encephalomyelitis are closely related to, if not identical with, acute multiple sclerosis.

Actually, the correlation between the clinical and the pathologic condition is still indefinite. Information is needed on the pathologic picture in cases of multiple sclerosis with a rapid fatal course. It is the purpose of this paper to review the histopathologic changes associated with the acute clinical course of the disease in an effort to clarify terms and to correlate more closely clinical and pathologic observations, in the hope that thereby a better basis may be had for a clinical approach to the problem.

ACUTE MULTIPLE SCLEROSIS

CASE 1.— A woman aged 35 had as initial symptoms of the disease diplopia, drowsiness and pronounced ataxia. A few days later she vomited and complained of dizziness and impairment of hearing. During the third week of her illness there rapidly developed dysarthria and dysphagia and spastic paresis of all the extremities. In the last three days of life there was complete flaccid paralysis of the lower limbs. The clinical course was extremely rapid, death occurring in three weeks.

Autopsy.—A limited number of irregular, disseminated foci of demyelination were observed. Two lesions were localized in the spinal cord; a few more were scattered in the medulla, pons and midbrain. Figure 1 *A* and *B* illustrate areas of destruction of myelin in the spinal cord. They were sharply circumscribed, completely devoid of myelin sheaths and scattered with apparent irrelevance. The large plaque in the spinal cord was located in both the white and the gray matter. The demyelinated patches exhibited increased cellularity in sections stained with cresyl violet, the foci consisting for the most part of large accumulations of gitter cells separated by glia fibers (fig. 2). The gitter cells were accompanied by numerous myelophages, which harbored debris of myelin within their large vacuoles. In the peripheral areas of the patches the predominating cells, besides the gitter cells, were cytoplasmic astrocytes inter-

From the Neurological Service and the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

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2. Marburg, O.: Die sogenannte akute multiple Sclerose (Encephalomyelitis periaxialis scleroticans), Jahrb. f. Psychiat. u. Neurol. **27**:213, 1906.

3. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

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mingled with microgliocytes. The latter as a rule appeared as rod cells, and with high power magnification it was possible to demonstrate their divided and subdivided polar processes. The cytoplasmic astrocytes were usually present in the marginal areas of the patches bordering on the white matter. In some areas they were mixed with a few fibrillary astrocytes, most of which showed clasmatodendrosis. Progressive proliferation of fibrillary astrocytes was not observed.

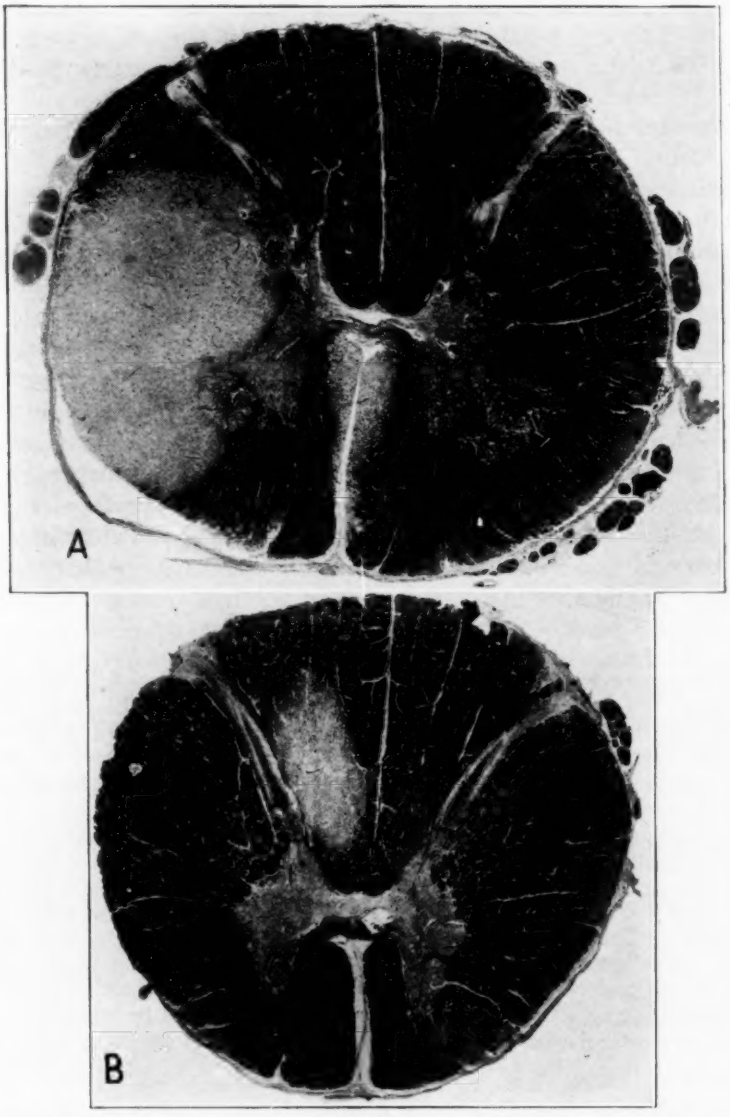

Fig. 1 (case 1).—*A*, sharply circumscribed areas of destruction of myelin in the spinal cord. *B*, small area of demyelination in the right dorsal column. Weigert-Pal stain for myelin sheaths; × 8.

In areas in which the gray substance was involved the ganglion cells exhibited severe degenerative changes. These varied from swelling and chromatolysis to vacuolation, liquefaction and complete dissolution. In some areas ganglion cells could not be detected even after careful search, and here white matter could not be differentiated from the gray substance.

In Bielschowsky preparations well preserved axons were encountered only occasionally. They were usually limited to the marginal areas of the patches. As a rule the majority of the nerve fibers were destroyed.

The blood vessels exhibited stasis. Most of the capillaries were distended and engorged with blood. In some of them occlusive changes could be traced. These consisted of complete filling of the vascular channel by a plug of cells mixed with pigment and a few coarse strands of fibrin. In some areas, usually within the marginal zone of the lesion, there were some newly formed capillaries, represented by endothelial budding. Many of the smaller blood vessels harbored in their distended perivascular spaces accumulations of gitter cells, which were occasionally mixed with a small number of lymphocytes. The leptomeninges appeared normal.

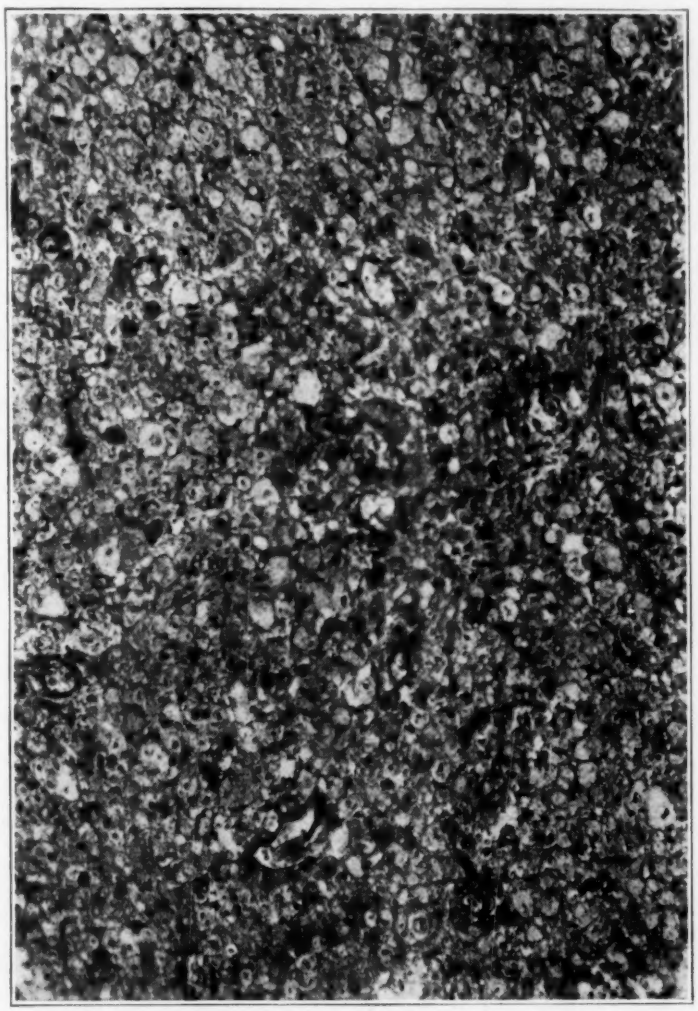

Fig. 2 (case 1).—Large accumulation of gitter cells in the demyelinated patches. Cresyl violet stain; × 175.

Case 2.—A girl aged 18 years complained of paresthesias and shooting pains in the right leg for four months previous to her admission to the hospital. Three months later sudden paralysis of the right lower extremity developed. After an interval of a few days complete paralysis of the left leg and incontinence of urine and feces were noted. Two weeks previous to admission to the hospital she noted paralysis of the right arm. The outstanding neurologic manifestations, six months after the onset, were complete flaccid paralysis of the lower limbs, paresis of the right upper extremity, tremor, ataxia in the left arm, scanning speech and nystagmus. Death occurred six months after the first symptom.

Autopsy.—Numerous areas of destruction of myelin were noted in the cord, brain stem, cerebellum and cerebral hemispheres. The lesions involved the gray and the white matter

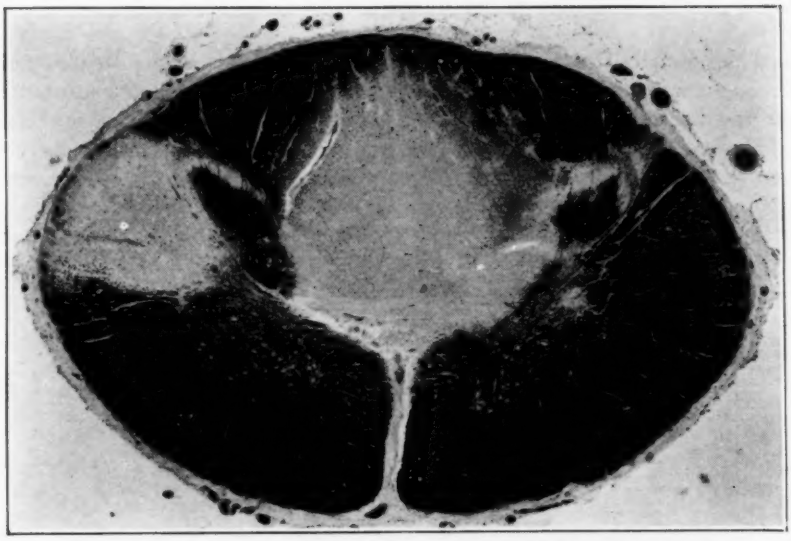

Fig. 3 (case 2).—Two large areas of complete loss of myelin in the spinal cord. Weigert-Pal myelin sheath stain; × 6.

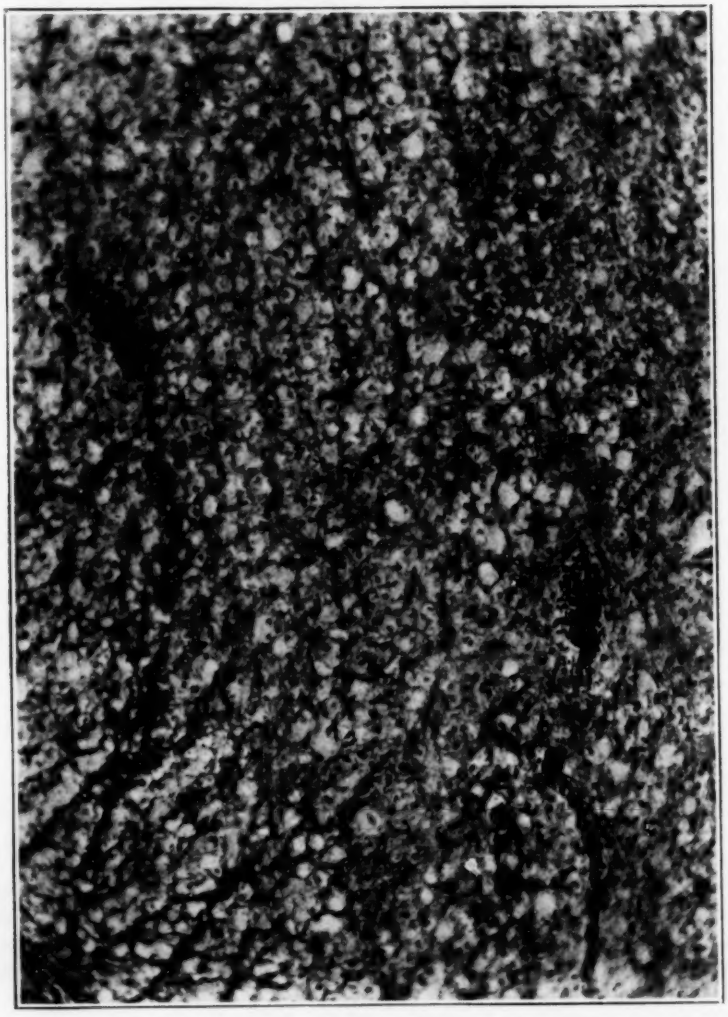

Fig. 4 (case 2).—Large accumulation of gitter cells in the demyelinated patches. Cresyl violet stain; × 175.

indiscriminately. A detailed histologic analysis of the lesions revealed changes similar to those described in case 1; they differed chiefly in degree.

The fundamental feature consisted of circumscribed areas of acute necrosis of the nerve tissue. The reactive cells were mostly compound granular corpuscles. Sections stained for myelin sheaths revealed varying degrees of demyelination. Figure 3 illustrates two large areas of complete loss of myelin in the spinal cord. They were sharply circumscribed and involved the gray and the white matter.

Staining with hematoxylin and eosin and with scarlet red revealed the presence of large masses of gitter cells in the patches (fig. 4). The cresyl violet preparations showed the

Fig. 5 (case 2).—Increased cellularity and perivascular cuffing in areas of demyelination. Cresyl violet stain; × 146.

increased cellularity of the affected areas (fig. 5). With high magnification it was possible to demonstrate enormous masses of gitter cells and myelophages and some cytoplasmic glia cells. In the Cajal preparations a moderate number of fibrillary astrocytes were seen at the periphery of the patches. Many of them were degenerated; their cytoplasm was swollen, and their dendrites were broken.

In Bielschowsky preparations the majority of the patches revealed severe axonal degeneration. The disappearance of a large number of nerve fibrils was manifested in numerous areas.

The lesions of nerve cells within the patches varied from acute swelling to the most severe type of degeneration, described by Nissl as liquefaction. Here and there nerve cells displayed ischemic changes, consisting of shrinkage of the cell body, disappearance of the Nissl granules and deformity of the nucleus.

The majority of the vessels were engorged; some were thrombosed. Many vessels were infiltrated with large masses of gitter cells and lymphocytes. Perivascular cuffing was especially notable in some of the patches in the spinal cord (fig. 5). In some areas the outline of the blood vessels was accentuated by the dense perivascular infiltration. Between the vessels the tissue presented a lacunar, spongy appearance. In areas in which it had taken place, repair was mainly by connective tissue formation, instead of by gliosis.

Two cases are described in which the course of illness, from the initial symptom until death, was three weeks and six months respectively.

The most conspicuous anatomic change consisted of diffusely scattered, typical plaques of loss of myelin, characterized by complete disintegration of nerve parenchyma in the form of circumscribed areas of softening and necrosis. An important feature was the complete absence of glial repair. In areas in which repair had taken place (case 2) limited proliferation of connective tissue, instead of the usual gliosis, was observed.

Fig. 6 (case 3).—Small cysts, due to complete softening of circumscribed areas of nerve tissue in the floor of the fourth ventricle. Hematoxylin-eosin stain; × 5.5

ACUTE LESIONS IN CASES OF CHRONIC MULTIPLE SCLEROSIS

Morphologically, chronic multiple sclerosis is characterized by the presence of old and more recent changes in different areas of the central nervous system (Steiner [5]). If the changes already described are specific and characteristic of the acute form of multiple sclerosis, one should be able to find similar histologic changes in some acute lesions occurring in cases of chronic multiple sclerosis. There follows the report of 2 cases of chronic multiple sclerosis with acute lesions.

Case 3.—A woman aged 39 with a typical history of the chronic, intermittent form of multiple sclerosis (sudden onset many years ago, with temporary blindness of the left eye) was admitted to the hospital two months previous to death because of a sudden exacerbation of her symptoms. She complained of sudden onset of diplopia, dizziness and disturbance of speech. Examination revealed typical signs of multiple sclerosis, including nystagmus, pallor of the temporal half of the optic disks, tremor, loss of the abdominal reflexes and spastic paresis of the lower extremities.

5. Steiner, G.: Krankheitserreger und Gewebsbefund bei multipler Sklerose, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **12**:268, 1931; Multiple Sklerose: Aetiologie, Pathogenese, pathologische Anatomie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **68**:289, 1933.

Autopsy.—Diffusely scattered old plaques of gliosis were observed. Microscopically, the majority of the plaques were characterized by entire destruction of myelin sheaths, preservation of the nerve fibrils and conspicuous glial fibrosis.

Besides these typical changes, a large area of tissue destruction localized in the floor of the fourth ventricle deserves a detailed description. Examination with low power magnification showed that the whole area (fig. 6) was spongy, because of the formation of numerous small vacuoles and cysts. These small cavitations were due to complete softening of circumscribed areas of tissue. In the remnants of softened tissue there were many gitter cells which contained masses of myelin, testimony to the acuteness of the process. Close examination showed that some of these small areas of softening contained a small central blood vessel, distended and partly occluded by thrombus. Some of the blood vessels were outlined by perivascular cuffing with gitter and mononuclear cells. The axis-cylinders, as well as the myelin sheaths, were destroyed. In the peripheral areas of the lesions, where the destruction of tissue was not so complete as in the central part, some axis-cylinders persisted, though they were distorted and damaged. All types of axonal change, such as varicosity, splitting and swelling, were present.

Repair in a few areas had taken place by the formation of new capillaries. No proliferation of fibrillary astrocytes and their fibers could be detected.

Case 4.—A man aged 34 complained of paresthesias in the upper and lower extremities and ataxia and weakness in both legs. After a few months there was notable improvement, which lasted five years. About three months previous to his death there suddenly developed rapidly progressing weakness of the lower extremities, associated with ataxia, dizziness, vomiting and headache.

The typical neurologic abnormalities of disseminated sclerosis were observed. During the stay in the hospital his speech became scanning, and decubitus and bronchopneumonia developed. He died three months after the final acute exacerbation and five years after the onset of his illness.

Autopsy.—Numerous old and recent lesions were seen. The former consisted of large patches of demyelination, localized particularly around the fourth ventricle and the aqueduct of Sylvius and in the spinal cord. Microscopic examination of these patches revealed old sclerotic lesions, characterized by complete loss of myelin, partial preservation of axis-cylinders and proliferation of glia and fat-laden cells.

Strikingly different were the recent lesions observed in the cerebellum and the midbrain. An instructive area is illustrated in figure 7 *A*, taken from the midbrain, in which there was observed a large focus of complete loss of myelin, the central portion of which contained a small circumscribed area of complete destruction of tissue. Microscopic examination revealed that complete disintegration of all elements of the nerve tissue, including the glia, had occurred in this area. Masses of gitter cells, many of them containing debris of myelin, were seen in the walls of the small cysts. The majority of the blood vessels showed gross dilatation and beadlike irregularity of their walls. Many of the vessels at the periphery of the plaque exhibited an abnormal degree of filling with blood. Some of the engorged vessels were cuffed with small perivascular hemorrhages. Occasionally the blood vessels were surrounded by small accumulations of gitter cells, filled with blood pigment. In the area of softened tissue there were a few small occluded blood vessels. Their lumens were plugged with fibrin and large masses of platelets.

Sections stained by the Cajal method showed loosening or complete dissolution of the glial reticulum. Only at the periphery of the lesions was there a moderate degree of proliferation of protoplasmic glia cells.

A different picture is illustrated in figure 7 *B*, in which irregular, concentric rings of normal and demyelinated tissue are observed in a focal area of plaque formation. Lesions of this type have been described in cases of acute multiple sclerosis by Marburg,[2] Steiner,[5] Barré and van Bogaert,[6] Hechst,[7] Hallervorden and Spatz[8] and others. Baló,[9] under the term "encephalitis periaxialis concentrica," described the lesion as a special pathologic syndrome.

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6. Barré, J., and van Bogaert, L.: Contribution à la dissociation anatomique et clinique des leuco-encéphalites subaiguës. Le type concentrique de Baló, Rev. neurol. **1**:547, 1933.

7. Hechst, B.: Zur Frage der akuten multiple Sklerose, Arch. f. Psychiat. **100**:491, 1933.

8. Hallervorden, J., and Spatz, H.: Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen, Arch. f. Psychiat. **98**: 641, 1933.

9. Baló, J.: Encephalitis Periaxialis Concentrica, Arch. Neurol. & Psychiat. **19**:242 (Feb.) 1928.

It seems clear that this concentric type of demyelination represents nothing specific. It occurs in cases of acute (Hechst [7]) and chronic multiple sclerosis (Steiner,[5] Sträussler and Scheinker [10]), as well as in some cases of diffuse sclerosis (Waggoner and Löwenberg [11]).

Two cases are described in which the clinical picture was characterized by a chronic progressive course of years' duration associated with an acute exacerbation a few months previous to death.

The pathologic process consisted of (*a*) a large number of typical old plaques of multiple sclerosis and (*b*) a few recent lesions in the form of circumscribed

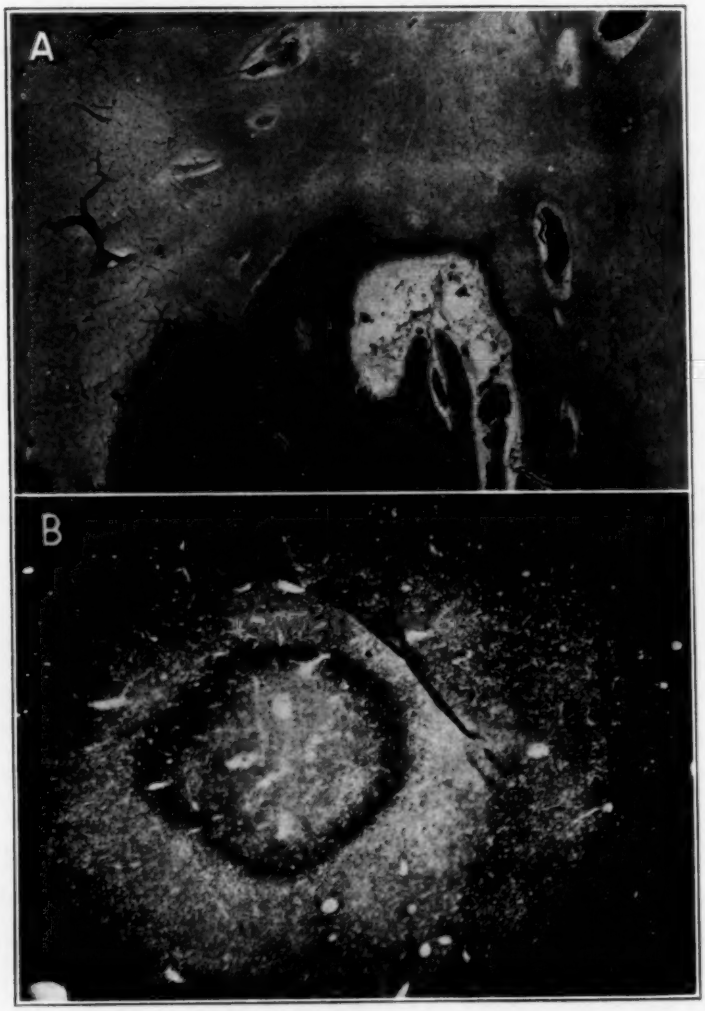

Fig. 7 (case 4).—*A*, large plaque of demyelination in the midbrain; circumscribed area of softening, with complete disintegration of all elements of the nerve tissue, including the glia. Weigert-Pal stain for myelin sheaths; × 5.5. *B*, concentric type of plaque formation, with irregular concentric rings of normal and demyelinated tissue. Spielmeyer stain for myelin sheaths; × 10.

areas of softening and necrosis. The latter were similar to the foci described in cases of acute multiple sclerosis.

10. Sträussler, E., and Scheinker, I. M.: Zur Pathologie der multiplen Sklerose, Monatschr. f. Psychiat. **91**:121, 1935.

11. Waggoner, R., and Löwenberg, K.: Konzentrische Sklerose, Arch. f. Psychiat. **101**: 184, 1933.

COMMENT

Cases similar to cases 3 and 4 may be found in the literature. Wohlwill [12] described a patient with the chronic form of multiple sclerosis who one month previous to death experienced a sudden exacerbation of symptoms. Transverse myelitis suddenly developed. Autopsy revealed the presence of a large area of softening involving the lower thoracic and the lumbar segments of the spinal cord. It is of interest to note that in the marginal zone of the affected area, instead of glial repair, there was proliferation of mesodermal tissue in the form of new capillaries (*Capillarsprossenbildung*).

A somewhat similar sequence was reported by Juba [13] in a patient with long-lasting spastic paresis of the lower extremities, in whom five days previous to death complete flaccid paraplegia suddenly developed. In Spielmeyer preparations of the lumbosacral segments of the spinal cord the typical patches of demyelination of multiple sclerosis, with cavity formation in their central areas, were observed. The cavitation was due to softening, necrosis and complete disintegration of all tissue elements. The author presented his case as that of an unusual malignant exacerbation occurring in the course of chronic multiple sclerosis.

Lesions similar to those observed in cases 1 and 2 in my series have been described by Hassin and Bassoe [14] as characteristic of "multiple degenerative softening." The main histologic features in their cases were the simultaneous destruction of the myelin and the axons, the prevalence of the microglial reaction and the vast extra-adventitial destruction of the nerve parenchyma. To these authors the presence of "multiple degenerative softening" differentiates these lesions from the lesions of multiple sclerosis.

Morphologic Comparison of Lesions of Acute and of Chronic Multiple Sclerosis.—The acute lesions in cases of chronic multiple sclerosis are identical with those observed in cases in which the clinical course assumes a fulminating character and terminates early in death. In the following paragraphs an attempt is made to compare the acute and the chronic lesion, allowance being made for the average variation in each.

Changes in the Myelin Sheaths.—The demyelinated plaques in chronic lesions of multiple sclerosis are characterized by their clearly defined borders and enormous variety in size, shape, demarcation and number; the plaques are usually entirely devoid of myelin, and their distribution is not limited to particular structures of the central nervous system. So far the lesions described and illustrated in cases 1 and 2 of my series (figs. 1 *A* and 3), in which the course from the initial symptom to death was three weeks and six months respectively, correspond entirely with those of the chronic form. They reveal the cardinal feature of distinctive plaques of loss of myelin which distinguishes multiple sclerosis from any other demyelinating disease.

Changes in the Axis-Cylinders.—As has been universally recognized, the lesions of chronic multiple sclerosis are generally characterized by selective destruction of the myelin sheaths. The persistence of axons is considered to be a cardinal point

12. Wohlwill, F.: Nicht-eitrige Entzündungen des Zentralnervensystems, in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1925, vol. 10, p. 455. Zwei seltene Komplikationen bei multipler Sklerose, J. f. Psychiat. u. Neurol. **37**: 408, 1928.

13. Juba, A.: Die maligne Exacerbation der multiple Sklerose, Arch. f. Psychiat. **109**:727, 1939.

14. Hassin, G. B., and Bassoe, P.: Multiple Degenerative Softening Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:613 (May) 1922.

in the pathologic picture of this disease. Yet in a series of recent studies by Putnam and Alexander [15] and others, it has been shown that the axons seldom remain undamaged.

In a recent series of investigations of early lesions in 20 cases of multiple sclerosis [16] the presence of the following types of lesions of the nerve fibrils was disclosed: (1) plaques in which the axis-cylinders were completely destroyed; (2) plaques in which the axis-cylinders were more or less severely damaged and reduced in number, and, finally, (3) plaques with fairly well preserved or substantially intact axis-cylinders. Whereas in the cases of chronic multiple sclerosis the last type was the most common, in the cases of acute multiple sclerosis the first two types, in the form of complete destruction or severe damage of the axis-cylinders, were predominant. There was nothing selective about the destructive phenomena in these lesions; the myelin, as well as the nerve fibers, disappeared as part of the general disintegration of tissue. The intensity of destruction of the axis-cylinders is presumably greater the more sudden and severe the onset of the lesion, in contrast to the milder and chronic lesions of disseminated sclerosis.

Changes in the Glia.—The glial scar is usually considered as one of the most fundamental features of the lesions of multiple sclerosis. Representing a terminal phase of scar formation, it is devoid of any specific significance and is of little help in interpretation and evaluation of the disease process.

Of greater significance are the early glial changes, which have not been stressed enough in the literature. They have been described in detail in a previous paper.[16] Three types of glial reaction were observed: (1) Pronounced rarefaction and loosening of the glial reticulum, with loss of stainability and a spongy appearance of the affected areas. In some plaques the tissue contained vacuoles, which usually harbored myelophages and gitter cells. In Cajal and Holzer preparations the neuroglia appeared greatly degenerated in the central part of the lesion. Occasionally there was a slight increase of connective tissue in the form of coarse fibers, which seemingly originated from the blood vessel walls. (2) Conspicuous proliferation of glia cells. In some of the patches Hortega preparations revealed the presence of numerous microglia cells, with their partial transformation into compound granular cells. Other patches contained numerous gitter cells, which were mixed with occasional cytoplasmic glia cells. Astrocytes were rarely observed. Their presence was usually confined to the marginal areas of the patches. More numerous were the cytoplasmic glia cells, which occasionally appeared as monster cells. (3) Glial fibrosis, which could be observed in the early lesions only occasionally.

When one compares these glial changes with those described in my cases of acute multiple sclerosis, one cannot escape the conviction that the lesions are similar, if not identical. The glial reaction as observed in my cases of acute multiple sclerosis consisted of a large accumulation of gitter cells and proliferation of microglia elements, mixed with a small number of protoplasmic glia cells. This cellular reaction was associated with a slight proliferation of connective tissue. There was almost complete absence of glial repair.

Perivascular Infiltration and Inflammatory Phenomena.—In the various descriptions of the lesions of multiple sclerosis there is variance as to the role

15. Putnam, T., and Alexander, L.: Changes in Axis-Cylinders and Other Parenchymal Structures in Multiple Sclerosis and Allied Conditions, Arch. Neurol. & Psychiat. **42**:1179 (Dec.) 1939.

16. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: I. Significance of Vascular Changes, Arch. Neurol. & Psychiat. **49**:178 (Feb.) 1943.

of lymphocytes in perivascular infiltrates. In a series of 93 cases Steiner [5] observed in every instance adventitial infiltrations of lymphocytes. On the other hand, Hassin [17] expressed the belief that the presence of lymphocytes in cases of multiple sclerosis is only accidental, and secondary to the presence of gitter cells. Also, Putnam [3] claimed that lymphocytic infiltrations in cases of multiple sclerosis are rare. In about one third [16] of my 20 cases of chronic multiple sclerosis perivascular infiltration could be seen. The majority of the cells were identified as gitter cells, mixed with microglia elements. Larger accumulations of lymphocytes were seldom observed.

Much more extensive were the perivascular phenomena in my cases of acute multiple sclerosis. Larger accumulations of lymphocytes were often observed. But in these cases, also, variation in lymphocytic infiltration was present, not only from case to case but from lesion to lesion in the same case.

Vascular Changes.—The genetic relation between the cerebral vascular system and the lesions of multiple sclerosis has been described in a previous paper.[16] In my cases of acute multiple sclerosis were observed vascular changes, congestion, stasis and occasional thrombus formation, similar to those described in cases of the chronic form.

In the light of my own observations and those reported in the literature, it seems clear that the acute and the chronic form of multiple sclerosis form a nosologic unit. The structural differences between the two can be explained by three factors: (1) the intensity and duration of the morbid process; (2) its acuteness or chronicity, and (3) the resistance of the organism.

As has been emphasized before, the fundamental feature of acute multiple sclerosis is that the lesions are not confined to the myelin sheaths and there is no proliferation of glial fibrils. Whereas the chronic lesions are generally characterized by a more selective destruction of myelin associated with pronounced glial repair, the acute lesions appear, as a rule, as a generally destructive and more malignant process, in which all tissue elements are severely damaged. The myelin sheaths, as well as the nerve fibers and the glia, disappear as a part of the general tissue disintegration. The acuteness of the process precludes glial fibrosis. The intensity of the tissue destruction seems, as a rule, to be greater the more acute and severe are the onset and course of the morbid process.

To consider acute and chronic multiple sclerosis as distinct morbid entities only because of the aforementioned structural differences is not proper, as it would not be proper to differentiate chronic fibroid phthisis of the lungs as a nosologic unity from "galloping consumption" because of the evident discrepancy of their histologic features. When one compares the morphologic conditions observed in the two forms of pulmonary tuberculosis with those of the acute and the chronic form of multiple sclerosis, one cannot escape the conviction that from the point of view of classification the conditions are identical: In chronic fibroid phthisis the predominant pathologic feature consists of massive proliferation of a mature fibrous tissue, with final scar formation and calcification. There is no evidence of acute lesions in the form of tubercles. Owing to a pronounced degree of resistance of the host to the presence of the organism, fibrosis and healing predominate. "Galloping consumption" can be compared to the acute form of multiple sclerosis. The entire disease may run its course in a few weeks; the resistance of the patient to the organism is very slight. The process spreads throughout the lungs with

17. Hassin, G. B.: Disseminated Encephalomyelitis (Meningo-Encephalomyeloradiculitis) Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **40**:1111 (Dec.) 1938.

great rapidity. Histologically, there are rapid caseation and necrosis of the lung tissue, with little or no reaction in the form of fibrous tissue formation. There is extensive destruction of elastic tissue. It is generally known that in many infectious processes, frequently because of the high virulence of the invading organisms or the lowered local immunity of the host, the clinical course assumes a fulminating character, terminates early in a fatal issue and thus precludes the evolution of the defensive reaction. This may be true in multiple sclerosis as well.

SUMMARY

The essential features of the acute lesions of multiple sclerosis may be summed up as follows:

Macroscopically the patches appear as small areas of softening and necrosis. Microscopically they are characterized by (1) a destructive process in which myelin sheaths as well as axis-cylinders are severely damaged; (2) formation of circumscribed areas of softening and necrosis; (3) excessive cellularity, due to an abundance of gitter cells mixed with lymphocytes and cytoplasmic glia cells; (4) absence of glial fibrosis; (5) a slight degree of repair through moderate proliferation of connective tissue, and (6) pronounced congestion and thrombosis of small veins.

Lesions closely resembling those described in cases of acute multiple sclerosis have been observed in typical cases of chronic multiple sclerosis in which an acute exacerbation of the clinical symptoms preceded death.

The view is expressed that the acute and the chronic form of multiple sclerosis are varieties of the same morbid entity. The structural difference in their lesions can be explained by the difference in intensity and duration of the same morbid process.

Cincinnati General Hospital.

ELECTRICAL EXCITATION OF THE CEREBRAL CORTEX

DESCRIPTION OF A NEW STIMULATOR

W. E. RAHM JR.
NEW YORK
AND
MAJOR JOHN E. SCARFF
MEDICAL CORPS, ARMY OF THE UNITED STATES

Electrical stimulation of the exposed cerebral cortex at the operating table is increasingly employed by neurosurgeons for purposes of orientation in routine work. The present paper, after a brief historical and critical survey of the stimulator needed in neurosurgery, describes a new stimulating unit designed by one of us (W. E. Rahm Jr.). It has been found by the other (Scarff) to have certain advantages over other instruments, both for practical use and in a number of physiologic aspects.

HISTORICAL AND CRITICAL REVIEW OF METHODS

In 1870 Fritsch and Hitzig [1] applied galvanic current to the exposed cortex of dogs and observed focal responses in the contralateral extremities. Their report constitutes a great landmark in neurophysiology, for until then there had existed profound and active disagreement between the leading schools of "physic" and philosophy as to whether localization of function was present in the brain. Fritsch and Hitzig demonstrated beyond question that such localization exists, at least for motor function.

The galvanic current, such as was used by Fritsch and Hitzig, is the simplest type of current available for purposes of physiologic stimulation. This current is produced by opening and closing a switch which connects the stimulating electrodes to a source of direct current, such as a storage battery or a dry cell. Since stimulation is dependent on the rate of change of the applied voltage, stimulation occurs only on the "make" and the "break," at which time the current either rises or drops sharply. Nothing whatever happens if the switch is left closed, since the current achieves a constant, and hence nonstimulating, value after the initial surge. The amount of stimulating voltage, of course, depends on factors determining the strength of current, such as the number of batteries used. A simple sketch of the circuit of this type of current is presented in figure 1 *A*, and the wave shape of galvanic current, photographed directly from a cathode ray oscillograph is shown in figure 1 *B*.

In 1873 Ferrier [2] reported for the first time on the electrical stimulation of the brain (of animals) with faradic current. His results confirmed in all particulars the fundamental observation of Fritsch and Hitzig that focal representation

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From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Fritsch, G., and Hitzig, E.: Ueber die electrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med., 1870, pp. 300-332.

2. Ferrier, D.: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lun. Asyl. Rep. **3**:30-96, 1873.

of motor function exists in the brain. Curiously enough, however, Ferrier's observations were fiercely attacked by Hitzig on the ground that with the faradic type of electric stimulus it would be impossible to confine the irritation to limited districts of the cortex cerebri. Hitzig contended that the muscular contractions which attended Ferrier's method of stimulation were due, in part or entirely, to irritation of nerve masses lying more deeply buried in the brain.

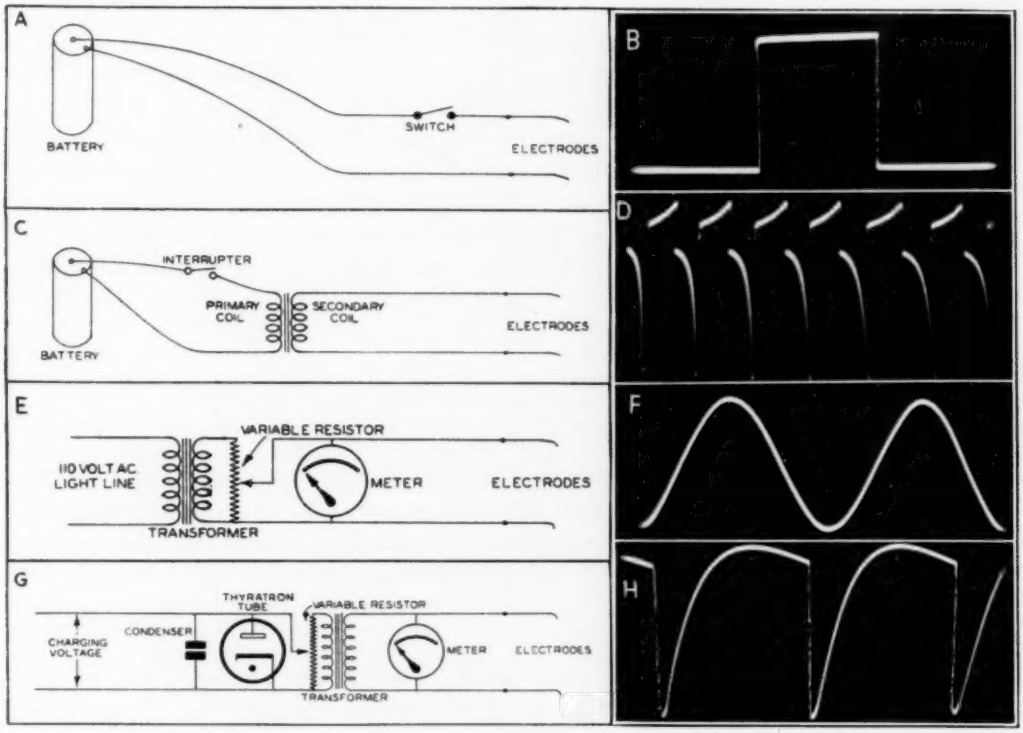

Fig. 1.—*A*, circuit diagram of a simple galvanic stimulator.

B, changes in voltage produced by "making" and "breaking" a simple galvanic current, from a photograph made with the aid of a cathode ray oscillograph. Note the abrupt rise and fall in potential. This produces an excellent stimulus.

C, circuit diagram of a simple inductorium of the type commonly used in physiologic laboratories to produce faradic currents.

D, changes of voltage occurring with the usual faradic current, as obtained from a simple inductorium. Neither the frequency nor the strength of the individual stimuli are constant, nor can they, from a practical point, be quantitated or controlled.

E, circuit diagnosis of a modern alternating current stimulator, having the common commercial electric line as a source of power.

F, the sine wave of the alternating currents obtained from the standard commercial power lines. The frequency of the changes in voltage is constant, 60 cycles per second being the rule. The voltage used can be accurately regulated by a rheostat and a meter. Theoretically this type of stimulus may be criticized because the "wave front" is far from "perpendicular," the change in voltage being relatively gradual as compared with the change in voltage occurring with the galvanic stimulus (q. v.). From a practical standpoint, however, this type of stimulator has been found to be fairly satisfactory for routine clinical use.

G, circuit diagram of a simple thyratron stimulator.

H, type of stimulus obtained with a thyratron stimulator, expressed in terms of volts, photographed directly from a cathode ray oscillograph. Note that the voltage rises relatively slowly as the condenser is charging and then drops precipitately as the condenser discharges. This is the moment when the physiologic stimulus is released.

That this contention was wrong was shown by J. J. Putnam,[3] who, after localizing the motor points for movements with minimal faradic current, abolished the responses by undercutting the cortex. He was also able by using slightly stronger currents to stimulate the subcortical structures exposed by undercutting. It should be stated here that spread of the current, when it occurs, is due to the arrangement of the electrodes, especially when a stigmatic single electrode is used for stimulation, with a large "indifferent" electrode placed somewhere at a distance.

The first recorded electrical stimulation of the human brain was carried out with faradic current in 1874, just four years after the work of Fritsch and Hitzig, and only one year after the work of Ferrier on the brains of animals. Roberts Bartholow, a surgeon of Cincinnati, had a patient with a carcinoma of the scalp which had eroded away the bone beneath it. Bartholow plunged bipolar needle electrodes through the cancer and the defect which it had produced in the

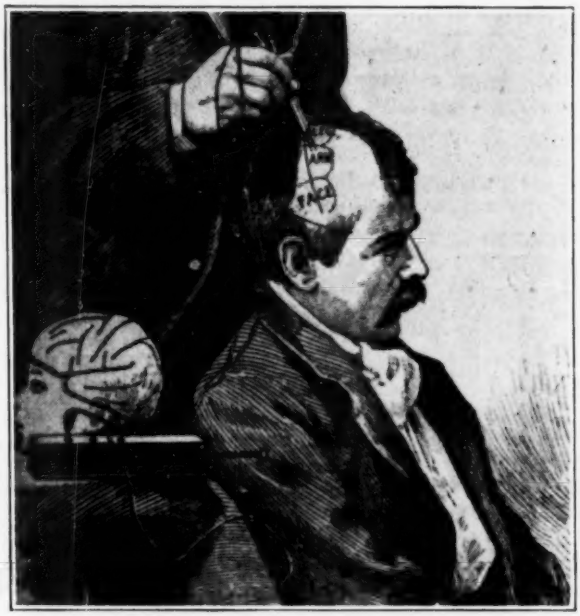

Fig. 2.—The earliest recorded stimulation of the human brain with an electric current was made in 1874 by Bartholow, of Cincinnati. He plugged needle electrodes directly into the brain through the scalp and a defect in the skull produced by a malignant growth and turned on the faradic current. Movements of the contralateral extremities were thus obtained. A similar bizarre experiment here pictured was carried out by Dana in 1893. The drawing accompanying Dana's original description is here reproduced.

skull, directly into the underlying cortex, and turned on a weak faradic current. Movements of the contralateral extremities were obtained. Crude as these experiments were, they served to confirm for man the essential truth established by Fritsch and Hitzig, and by Ferrier for animals, that motor function at least has focal representation in the cerebral cortex. Some twenty years later (1893) this curious method of "faradization" of the human brain was repeated by Dana [4] and recorded by him, with the interesting sketch here reproduced (fig. 2). Between

3. Putnam, J. J.: Contribution to the Physiology of the Cortex Cerebri, Boston M. & S. J. **91**:49-52, 1874.

4. Dana, C.: The Experimental Study of the Seat of Cutaneous Sensation, M. Rec. **43**: 578-579, 1893.

these two bizarre experiments, however, Sir Victor Horsley, of London, had already excited with faradic current the exposed human cerebrum at the operating table and had laid the cornerstone for truly scientific investigation of the human cerebral cortex by electrical stimulation. For those who may be interested, a detailed history of the localization of the primary motor centers in the brains of animals and of man has already been recorded elsewhere.[5] A diagram of the electric circuits in the inductorium is shown in figure 1 *C*. The character of the stimulus obtained from such an instrument, photographed directly from a cathode ray oscillograph, is shown in figure 1 *D*.

There are many objections to the use of the inductorium as a stimulator. The rate at which the clapper travels affects not only the frequency of the stimuli but the strength of the secondary, or stimulating current, and it may properly be deduced that the clapper does not travel at the same rate on any two successive days. Very small adjustments of the set screw on the clapper produce large changes in its rate of travel. Furthermore, the voltage produced by the secondary circuit depends not only on the number of batteries used in the primary circuit but on the freshness of the individual batteries. Also, the stimulating voltage is affected tremendously by the distance between the primary and the secondary coil, and this is difficult to measure accurately. In brief, for all practical purposes, quantitation of stimuli with the inductorium is impossible.

The advent of the alternating current generator produced another, and much better, form of frequency stimulator. In the stimulating units of this type, a transformer is employed to reduce the potential to about 10 volts, and a variable resistance is then added for further adjustments. Finally, a meter is connected directly across the leads going to the electrodes. The variable resistance may then be adjusted until the meter reads the desired voltage. Figure 1 *E* gives a rough diagram of the circuit of this type of stimulator, and figure 1 *F* shows the type of current produced.

The alternating current stimulator is simple, compact and accurate. It can be operated by any one. The rate of change, or alternation, is closely held to 60 cycles per second, which is an acceptable frequency for stimulation either of the cerebral cortex or of the peripheral nerves. Its constancy is in contrast to the irregular turning of the clapper on an inductorium. The voltage, which is the only variable, can be immediately read at any time, and can be adjusted easily by observing the meter. A stimulator of this type, built by one of us (W. E. R. Jr.), has been used by us on several occasions and has proved to be well adapted to the everyday, routine needs of the neurosurgeon, when elaborate studies in neurophysiology are not intended.

A great advance in the technic of electrical excitation followed the development of the thyratron. This instrument permits selection and control not only of the strength but of the rate of frequency of the stimuli used.

The essential feature of this instrument is a gaseous discharge (thyratron) tube. This tube is usually connected across a condenser, and a charging current is applied. While the condenser is absorbing the charging current, the thyratron remains nonconducting, but as the condenser becomes charged, the gas in the thyratron becomes ionized by the rising voltage. When this happens, the tube becomes conducting and short circuits the condenser. The condenser having lost its charge, the voltage drops and becomes too low to maintain the thyratron in an ionized state, so that the tube becomes nonconducting again and the condenser

5. Scarff, J. E.: Primary Cortical Centers for Movements of Upper and Lower Limbs in Man: Observations Based on Electrical Stimulation, Arch. Neurol. & Psychiat. **44**:243-299 (Aug.) 1940.

starts to charge once more (fig. 1 *G*). This cycle continues, with production of the wave shape shown in figure 1 *H*. The relatively slow rise represents the charging condenser; the sudden sharp drop, the discharge of the condenser by the ionized thyratron tube. When the charging current is held at constant voltage, the rate of oscillation is determined by the size of the condenser. The stimulating voltage is controlled by a variable resistance and is measured by a meter connected across the leads to the electrodes. A step switch is provided, so that a number of different condensers can be used. Since each of these condensers remains constant in its properties, it is possible to know in advance what frequency each condenser will give. By construction of a unit so that any one of a number of condensers

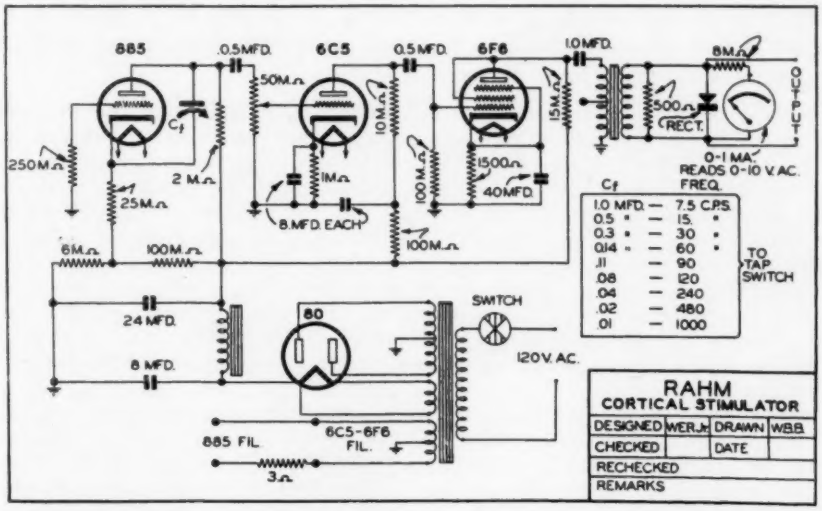

Fig. 3.—Circuit diagram of new stimulator. The apparatus consists primarily of eight different simple condenser and thyratron circuits, each with a different frequency of discharge, any of which may be selected for use. Another essential feature is the large amount of resistance introduced into the secondary circuits. This resistance, introduced between the stimulating bipolar electrodes by the cortex, thus becomes relatively insignificant.

Fig. 4.—Voltage curve of stimuli delivered by a simple thyratron stimulator when the resistance between the electrodes is changed. Compare with figure 1 *H*. This type of change in the stimulus has been corrected in the newly modified thyratron stimulator described in this paper.

may be introduced into the system as desired, a simple stimulator of variable frequency and of high accuracy and simplicity of operation will result.

A diagram of such a thyratron stimulator with a variable frequency is shown (fig. 3), together with the curve of the current produced by the instrument (fig. 4). Stimulation occurs during the fall of the potential; the more perpendicular the "face" of the fall, the more perfect the stimulus.

While the simple thyratron marks a great advance in the technic of physiologic electrical excitation, it is still not without considerable possibility of error when precise quantitation of strength and rate of stimulation is desired. For example, a

certain amount of power is required to stimulate the cortex. If the stimulator is incapable of delivering the requisite amount of power, the stimulating voltage will change the moment the electrodes touch the cortex. The inductorium is capable of developing practically no power; hence, when the electrodes are applied to the cortex the voltage drops enormously, and the wave form may change greatly. The same fault may often be found with the simple thyratron stimulator. With improvements in design and construction, however, most of these difficulties can be obviated.

DESCRIPTION OF NEW STIMULATOR

A new, modified type of thyratron has been developed and built by one of us (W. E. R. Jr.) which overcomes most of the errors inherent in older models. We have used it extensively in the operating room and have found it extremely satisfactory from all standpoints. A short, technical description and discussion of this new stimulator is here given.

The unit is designed around the type 885 thyratron. The circuit for this tube is conventional in design and provides by means of a step switch the following stimulus frequencies: 7.5, 15, 30, 60, 120, 240, 480 and 960 cycles per second. The frequency of the oscillator at various steps was determined by means of a cathode ray tube producing Lissajous figures by beating of the oscillator against the 60 cycle light line. In order that the stability of the oscillator may be insured and its frequency not be varied by either change in the loading of the oscillator or variation in the amplitude of the stimulus, the oscillator was followed by a 6C5 triode acting as a buffer. Oscillators of this design have been used previously, but in nearly all cases the amplitude of the stimulus was controlled by varying the voltage of the oscillator. This is impossible without the frequency of the oscillator being changed. Great care, therefore, was taken in designing this unit to prevent any direct or reflected changes in the oscillator circuit.

The cortex presents an impedance, the value of which depends greatly on its state of moisture and the separation of the electrode. However, an average value was assumed as 1,000 ohms for the usual bipolar electrodes separated by a few millimeters. The threshold of the motor cortex was found to be between 1.5 and 5 volts, which agrees with the observations of other investigators. Our own determinations of threshold were made by measurement of the voltage actually present at the stimulating electrode. It is apparent that a 6C5 triode does not have sufficient power to deliver 5 volts across a 1,000 ohm load. For this reason, the 6C5 triode was followed by a 6F6 power pentode amplifier. Control of the amplitude of the stimulus was achieved by placing a variable potentiometer in the grid circuit of the 6C5 triode. In order that any power may be delivered into the stimulating electrodes, it is necessary that output be of as low an impedance as possible. For this reason it is not possible to couple the electrodes to the plate circuit or the power amplifier by means of a coupling condenser, since the reactance of this condenser is high with respect to the resistance of the cortex and at the time of stimulation most of the voltage is developed across the condenser, and little across the stimulating electrodes. Therefore, an output transformer with an impedance of 500 ohms has been used. With this arrangement it is possible to deliver 10 volts across a 1,000 ohm load. As a result, there is almost no detectable drop in voltage when the bipolar electrodes are applied to the cortex. The amplitude of the stimulus applied to the cortex has been measured by means of a rectifier type of voltmeter connected across the electrodes, and the voltage of the stimulus measured has been found to be actually equal to the voltage of the administered current.

With this stimulator, it is possible in most cases to elicit movements by excitation of the human cortex with stimuli of 2 to 4 volts. This figure is in contrast to voltages reported by Penfield and Erickson,[6] who stated that they used up to 60 and 70 volts for stimulation. Such values, we believe, are incorrect, since if 60 volts was actually applied across the normally low impedance of the cortex, the tissue would be cauterized almost immediately. It is obvious that the stimulators used by these investigators were calibrated under no load conditions, and that the actual stimulating voltage ("root mean square or average") was much lower. However, this cannot be determined from their data.

6. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 531.

We have chosen to calibrate this stimulator in terms of voltage. Since the stimulator has good regulation, its output voltage will remain almost constant, regardless of fluctuation in the impedance of the cortex. If the stimulator were calibrated in terms of current, i. e., amperes, the readings would, of course, vary with changes in the impedance of the cortex. Technically, it is easier to maintain a constant voltage than a constant amperage. The correctness of this thesis is well borne out by the fact that in any given patient the same movement could always be elicited with a current of the same recorded voltage. This held true despite the fact that the cortex was often lavaged between stimulations, which, of course, caused decided change in impedance, and therefore in amperage—hence our decision to quantitate the stimuli in terms of volts, rather than of amperes.

This stimulator is simple in design. It is completely operated from the alternating current light line, without need of batteries; the amplitude of stimulus is

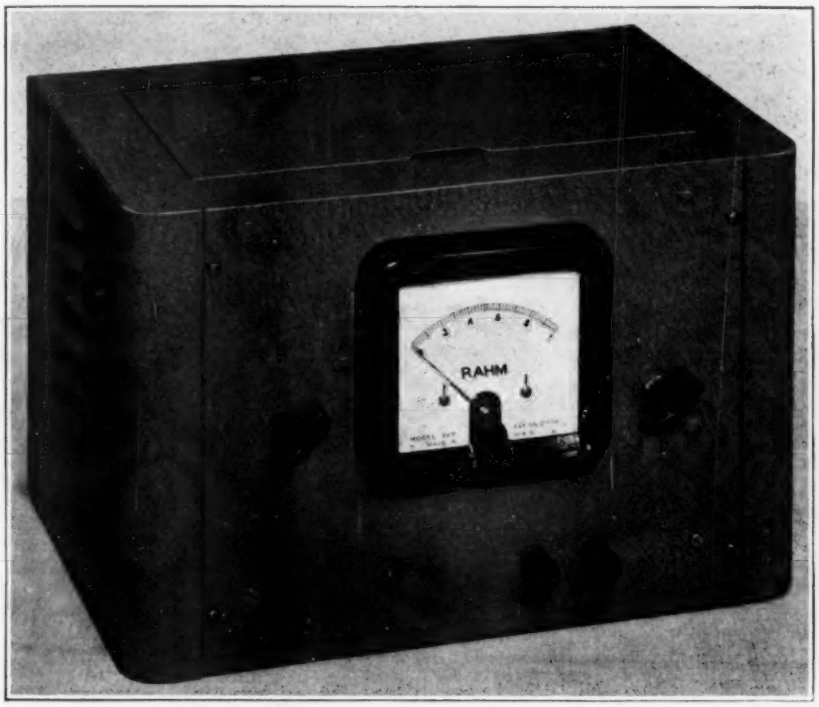

Fig. 5.—The new type of stimulator described in this paper is small, compact and simple to operate. The voltage of the individual stimuli can be selected and accurately controlled and can be read directly from a dial without necessity of calibration. The instrument also allows a choice of frequencies ranging from 7.5 to 960 stimuli per second.

easily controlled and is expressed directly in volts, rather than in dial settings, which need subsequent calibration. A wide range in frequency of stimuli is possible, and this can be predetermined and maintained with great accuracy. From a practical standpoint, the instrument is compact, rugged and easy to operate (fig. 5).

SUMMARY

1. A brief historical and critical review of the various technics used for electrical stimulation of the exposed brain is presented.

2. A new and improved type of thyratron stimulator is described.

Department of Neurology, Columbia University College of Physicians and Surgeons.

Clinical, Technical and Occasional Notes

NEGATIVE THERAPEUTIC EFFECT OF MASSIVE DOSES OF VITAMIN E ON AMYOTROPHIC LATERAL SCLEROSIS

VERN LAUER ZECH, M.D., AND IRA ROCKWOOD TELFORD, PH.D., WASHINGTON, D. C.

The early favorable reports of investigators [1] on the therapeutic use of vitamin E for certain neuromuscular diseases of uncertain origin have not been confirmed by more recent workers.[2] A careful survey of the literature on this controversial subject suggested to us that possibly prolonged massive doses of vitamin E (alpha tocopherol) [3] might be beneficial in these neuromuscular disorders. Wechsler [4] and Spies and Vilter [5] administered trial doses of 1,000 and 500 mg. respectively to

From the Department of Anatomy, George Washington University School of Medicine.

The patients discussed in this paper were referred to us for treatment by Dr. Walter Freeman and associates, of the department of neurology of the George Washington University School of Medicine.

1. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10-13 (Jan. 6) 1940. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**: 948-950 (March 16) 1940; The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765-778 (Dec.) 1940; Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, Arch. Neurol. & Psychiat. **45**:873-875 (May) 1941. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**:2187-2191 (June 1) 1940.

2. Sheldon, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha Tocopherol) Therapy in Certain Neurologic Disorders, Proc. Staff Meet., Mayo Clin. **15**:577-580 (Sept. 11) 1940. Fitzgerald, G., and McArdle, B.: Vitamins E and B_6 in the Treatment of Muscular Dystrophy and Motor Neurone Disease, Brain **64**:19-42 (March) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha Tocopherol), J. A. M. A. **116**:1893-1895 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, ibid. **116**:1895-1896 (April 26) 1941. Doyle, A. M., and Merritt, H. W.: Vitamin Therapy of Diseases of the Neuromuscular Apparatus, Arch. Neurol. & Psychiat. **45**:672-679 (April) 1941. McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy: Vitamin B_6, Other Factors of the B Complex, and Vitamin E, J. Pediat. **18**:727-731 (June) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**:258-264 (Aug.) 1941. Worster-Drought, C., and Shafar, J.: Motor Neurone Degeneration Treated with Vitamin E, Lancet **2**:209-212 (Aug. 23) 1941. Alpers, B. J.; Gaskill, H. S.; Cantarow, A., and Yaskin, H. E.: Effect of Vitamin E on Progressive Muscular Dystrophy and Amyotrophic Lateral Sclerosis, Arch. Neurol. & Psychiat. **46**:752 (Oct.) 1941. Schwarz, G. A.; Gammon, G. D., and Masland, R. L.: d-l Alpha Tocopherol Acetate (Synthetic Vitamin E) in Treatment of Various Neuromuscular Disturbances, ibid. **46**:752 (Oct.) 1941. Harvey, R. W., and Hume, P. B.: Vitamin E and Nervous Diseases, California & West. Med. **55**:293-295 (Dec.) 1941. Schwarz, G. A.; Gammon, G. D., and Masland, R. L.: Use of d-l, Alpha Tocopherol Acetate (Synthetic Vitamin E) in Various Neuromuscular Disturbances, J. Nerv. & Ment. Dis. **96**:286-295 (Sept.) 1942. Pohl, J. F., and Baethke, D.: Vitamin E in Progressive Muscular Dystrophy: Failure of Oral Administration in Fifteen Cases, Am. J. Dis. Child. **64**:455-461 (Sept.) 1942.

3. The alpha tocopherol and the thiamine hydrochloride used in this experiment were supplied by Merck & Co., Inc., Rahway, N. J., through the cooperation of Dr. D. F. Robertson.

4. Wechsler, I. S.: Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, Arch. Neurol. & Psychiat. **45**:873-875 (May) 1941.

5. Spies, T. D., and Vilter, R. W.: A Note on the Effect of Alpha Tocopherol (Vitamin E) in Human Nutrition, South. M. J. **33**:663-664 (June) 1940.

patients suffering from such disturbances. No apparent harmful effect on these patients was observed. We decided, therefore, to maintain a small series of patients under treatment with prolonged massive doses of alpha tocopherol, averaging as much as 1,000 mg. per day, for varying periods (twenty-three to one hundred and twenty days). Approximately one half of the daily dose was given intramuscularly in sterile peanut oil and the remaining amount was given orally in tablet form. In most cases therapeutic amounts of bile salts were given to

Summary of Cases

Case, Age, Color, Sex	Diagnosis	Initial Signs and Symptoms	Treatment and Duration	Total Amount of Alpha Tocopherol, Gm.	Results
1 56 yr. white male	Amyotrophic lateral sclerosis	Early stage: Muscular fibrillations, with advancing general weakness, unsteadiness of gait, initial atrophy of muscles of hands, followed by objective atrophy of all body muscles, especially extensors; little bulbar disturbance; exaggerated deep reflexes; Babinski sign	Alpha tocopherol: 60 Gm. over period of 60 days (0.5 Gm. intramuscularly and 0.5 Gm. orally a day); 30 Gm. over additional 60 day period (0.25 Gm. intramuscularly and 0.25 Gm. orally a day). Supplemental therapy: 15 mg. thiamine hydrochloride a day orally; bile salts, in therapeutic amounts, daily	90 Gm. over period of 120 days	No arrest of the progressive disease process; no toxic effects from vitamin administration; prognosis unaltered by treatment
2 63 yr. white male	Amyotrophic lateral sclerosis	Late stage: patient still ambulatory with aid of cane; generalized weakness, with progressive muscular atrophy; fibrillary twitchings; marked periodic bulbar attacks	Alpha tocopherol: 0.5 Gm. orally and 0.25 Gm. intramuscularly a day for 60 days; 0.5 Gm. orally a day for additional 30 days; 15 mg. of thiamine hydrochloride orally a day	60 Gm. over period of 90 days	Rapidly progressive process, terminating in death from bulbar paralysis; no toxic or beneficial effects from vitamin therapy
3 61 yr. white male	Amyotrophic lateral sclerosis	Early stage: exaggerated deep reflexes; progressive weakness; some atrophy of small muscles of hand; muscular fibrillations	Alpha tocopherol: 23 Gm. over period of 23 days (0.5 Gm. orally and 0.5 Gm. intramuscularly a day). Supplemental therapy: 15 mg. of thiamine hydrochloride orally a day; bile salts, therapeutic amounts, daily	23 Gm. over period of 23 days (treatment terminated, owing to lack of cooperation from patient)	Little change over period of observation; probably progressive decline; no toxic effects from vitamin therapy
4 42 yr. white male	Atrophy of right shoulder muscles due to disuse, probably on basis of former injury to shoulder (traumatic arthritis)	Pain in and extreme atrophy of muscles of right shoulder; normal use of right arm greatly reduced	Alpha tocopherol: 0.5 Gm. orally a day, and 0.25 Gm. intramuscularly three times a week for 60 days; 0.5 Gm. a day orally for additional 60 days; 15 mg. of thiamine hydrochloride daily; bile salts daily; heat and mild exercise	68 Gm. over period of 120 days	Complete return to normal use of right arm; no toxic effects from therapy

facilitate the proper absorption of the orally administered vitamin E. Supplemental daily doses of 15 mg. of thiamine hydrochloride were given orally to all patients.

We report here for the first time on the prolonged administration of such massive amounts of vitamin E to 3 patients suffering from amyotrophic lateral sclerosis, 2 of whom had an early stage and 1 a late stage of the disease. We also report the results of vitamin E therapy in a patient with localized muscular atrophy. This was possibly an atrophy of disuse, precipitated by moderately severe traumatic arthritis.

COMMENT

The inability of most investigators to secure favorable therapeutic results with alpha tocopherol in cases of amyotrophic lateral sclerosis is due, we believe, to

the fact that several etiologic factors are probably involved, vitamin E deficiency being only one of them. Additional factors may be: (1) failure of clinicians to use sufficiently large daily amounts of the vitamin; (2) inability of patients in the late stage of the disease to respond to treatment, although in the early stages a favorable response may be elicited; (3) too short a period of therapy; (4) poor absorption of the orally administered vitamin E from the gastrointestinal tract, with material reduction in the effectiveness of the drug, and (5) a synergistic action between vitamin E and vitamin B_1.

We have taken cognizance of these factors in our experiment. We used massive daily doses of alpha tocopherol (up to 1,000 mg. daily). We continued this large dose for a relatively long period (as long as one hundred and twenty days). Two of our patients were treated in the early stages of the disease. All the patients received an ample daily therapeutic supply of bile salts to facilitate the intestinal absorption of the vitamin. We made ample use of daily supplemental therapy with thiamine hydrochloride to promote any possible synergistic action of the two vitamins. This treatment with vitamin B_1 also ruled out any possible thiamine deficiency that might have contributed to the neurologic picture.

Although the therapeutic regimen which we instituted for our patients with amyotrophic lateral sclerosis took into account all these factors, the results were negative and discouraging. We hesitate to attribute the apparent cure of the patient with localized muscular atrophy (case 4) to the treatment with alpha tocopherol. This patient received, in addition to the vitamin E, daily diathermy and exercise therapy. This supplemental treatment may have relieved the probable arthritis, so that the patient was enabled to use his arm again and thus gradually build up the muscles that had become atrophic from constant disuse.

CONCLUSIONS

1. Massive doses of vitamin E (alpha tocopherol) had no effect on the progression of symptoms in this series of patients with amyotrophic lateral sclerosis.

2. A patient with localized muscular atrophy of uncertain origin was apparently cured after extensive vitamin E therapy.

George Washington University School of Medicine.

SPECIAL ARTICLE

THE SPECIAL HOSPITAL IN TIME OF WAR

WILDER PENFIELD, M.D.
AND
W. V. CONE, M.D.*
MONTREAL, CANADA

What we would say about special hospitals deals primarily with neurologic centers. The argument might be applied to orthopedic, plastic and perhaps other units in time of war. But because of the interests of this audience and the limitations of our own experience, we must approach the subject from the point of view of neurosurgeons, from that of adequate care of injuries of the nervous system.

SEGREGATION IN CIVILIAN HOSPITALIZATION

Neurology came into existence as the result of segregation of patients. In the shadow of the dome of the Salpêtrière Jean Charcot found a group of human derelicts, and among them all the chronic maladies of the nervous system. The Hospital for the Paralyzed and Epileptic provided Hughlings Jackson with a group of patients selected according to the symptom, as the name suggests, and he described the neurologic mechanisms involved in paralysis and epilepsy.

Neurosurgery was born when Horsley began to operate in a special neurologic hospital at Queen Square, London. Cushing gave the specialty a good name in his clinic, and he was followed by other members of this association: by Charles Frazier, in Philadelphia; by Charles Elsberg, at the New York Neurological Institute, and, in St. Louis, by Horsley's pupil, Ernest Sachs.

To neurologists these statements are truisms. All will agree that it was selection of patients and their segregation which made possible the birth of both neurology and neurosurgery, and today it is still true that neurosurgical and neurologic clinics cannot derive sufficient material from the unselected admissions to a general hospital. They must reach out independently to a wider population.

SEGREGATION IN MILITARY HOSPITALIZATION

The same principle should be applied to military populations. There are two reasons that it is unwise to attempt to create a neurosurgical clinic in every base hospital for the army and navy. First, there are not enough well trained neurosurgeons to make this possible. Second, if patients are admitted without selection to these base hospitals, there are not enough patients to form such a clinic. Furthermore, one neurosurgeon cannot build a special unit alone, however clever he may be. He must gather together personnel, equipment, laboratories and, most important of all, advisers.

It may also be added that if men in the armed services are to receive the care which they deserve, care equal to that received by the civilian population in large

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From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

*For two years, 1940 and 1941, lieutenant colonel, Royal Canadian Army Medical Corps, in charge of surgery at no. 1 Neurological Hospital, Canadian Army Overseas.

centers, such as San Francisco and Manchester, England, each area of combat must have one or more specialized centers for neurosurgical treatment, and the stream of wounded must be so handled as to transport patients needing this type of treatment directly to these hospitals whenever possible.

It is not enough to send general hospitals to combat areas and assume that one will be selected eventually for neurosurgical, another for orthopedic, another for plastic and still another for thoracic specialization. These special units are too important for that. They should be planned from the beginning, although of course it is quite feasible, and even desirable, to house each adjacent to some large general hospital. Furthermore, there must be special hospitals at home to receive and dispose of the patients with injuries to the nervous system. Failure to segregate these patients after their return to the homeland is quite inexcusable.

During great military activity all hospitals may have to accept some patients with injuries of the nervous system, and one of the surgeons in each hospital should, no doubt, have a working knowledge of neurosurgery, but such patients should then be shifted to the regional major neurosurgical unit. However, with well planned triage, that is, with routing of patients according to their individual needs, it is possible often to send them directly from the dressing station to the special hospital. With the development of evacuation of the wounded by air, selective triage becomes still more practicable.

In any combat zone a special neurologic hospital can provide consultation in neurology and neurosurgery for the other base hospitals in that area. It can also serve as a training center to take from each of the base hospitals a member of its staff for limited periods of concentrated experience and teaching. These men then return to the general hospital familiar with what neurosurgery can accomplish and prepared to recommend transfer or retention of patients for minor procedures, so that neurosurgical treatment over the whole area is rendered consistent.

COMBINATION OF NEUROSURGICAL AND NEUROLOGIC SERVICES

Finally, a special neurosurgical hospital should also be a neurologic hospital, where the nonoperative conditions of the nervous system are handled and where neuroses are treated quickly and the patients returned to duty. Only a small percentage of patients with such disorders will need to be placed in a lower category or shifted to another branch of the service, provided they are treated while their disorder is still fresh. This combination of neurologic and neurosurgical services adds immeasurably to the effectiveness of the whole hospital.

During the long periods of inactivity, which are inevitable in most campaigns, neuroses flourish and multiply. During periods of active combat, functional complaints decrease, and the neurosurgical service accepts the majority of patients. At all times the two groups can be mutually helpful. The laboratories of neuropathology, cerebrospinal fluid chemistry, radiology and electroencephalography, all serve the neurologist and the neurosurgeon equally. Furthermore, the professional interplay is good for the wit, and no doubt the soul, of each.

COORDINATION WITHIN COMBAT ZONE

Let it be granted that the injuries of the nervous system are best treated by specialists. It then follows that for a combat zone a principal neurosurgical consultant and a principal neurologic or neuropsychiatric consultant should supervise the neurosurgical and the neurologic treatment throughout that area. Such a consultant should be able to recommend the transfer of medical officers from the neurologic center to base hospitals, or even field ambulances, for periods of service.

He would recommend what type of patients should be transferred or kept in any unit. He should further supervise the steady flow of new medical officers through the neurologic center for the special training which they most need.

TRAINING OF SPECIALISTS FOR WAR

Rapid training of so-called specialists for the army in a few months at the very best hospital is estimable. But it is a farce if such men are to be sent out as independent experts. They would be a menace in civilian practice. They might well prove the same in military practice. But if these men receive a little training in an area and are used at the discretion of a leader in their new specialty; if they are placed by him and advanced on his recommendation with further learning, then their work can be controlled, and these medical officers will grow in knowledge of the specialty as the result of continued stimulation. This is what happened to a group of men who were fortunate enough to work under the leadership of Robert Jones [1] during World War I. A distinguished group of orthopedists today may well bear testimony to the efficacy of this system.

1914-1918

There is nothing original in these proposals. At the close of the last war, Harvey Cushing [2] expressed his regret that the British,[3] with all of their knowledge of neurology, had not segregated their neurologic patients (overseas). He pointed out that the French had created a *centre neurologique* for each army. The Americans with a scant six months of actual combat and with an army that mushroomed from nothing to 2,000,000 men, had not had time, perhaps, to put into execution their ambitious scheme of (*a*) forward-situated neurosurgical teams, (*b*) an intermediate zone of scattered neurosurgeons and neurologists and, finally, (*c*) neurologic centers, where neurologists, neurosurgeons and orthopedists would work together in a harmony of reconstructive effort. However, Cushing [4] pointed out that in the next war such a scheme might not work out at all. "The next war," he said, "like as not, will be largely in the air, with the first blows struck in what we today term the base."

TODAY

This war *is* different. Mobile neurosurgical teams, with all of their equipment housed in trucks, have been tried out in France and Libya by the British and, we understand, have not proved altogether satisfactory. On the other hand, distant evacuation by air of patients with head injuries has proved its value. The Germans delivered such casualties from Poland to Breslau, Germany, and from France to a special neurosurgical hospital in Brussels, Belgium; the British, from North Africa to Cairo, Egypt.

Great Britain, in the wartime reorganization of the whole hospital system that was forced on her by the threat of invasion and the bombing of her cities, has created under the Emergency Medical Service many special hospitals and units, the number of which eighteen months ago was roughly as follows: for orthopedics, 21; for neurosurgery, 11; for peripheral nerve surgery, 3; for thoracic surgery, 10, and

1. Consultant to the War Office in Orthopaedics during the war of 1914-1918.

2. Cushing, H.: Neurological Surgery and the War, Boston M. & S. J. **181**:549 (Nov. 6) 1919.

3. It is true that in France, toward the end of the war, spontaneous segregation of patients had begun under Adie, under Wagstaffe and under Geoffrey Jefferson.

4. Cushing, H.: Some Neurological Aspects of Reconstruction, Arch. Neurol. & Psychiat. **2**:493 (Nov.) 1919.

for plastic surgery, 9, not to mention centers for care of patients with neuroses, and other units. These centers deal with military, as well as civilian, casualties. The neurosurgical centers are coordinated and supervised by Mr. Geoffrey Jefferson, consultant adviser to the Emergency Medical Service and honored guest of the American Neurological Association.

At the same time, the services have established a few special hospitals of their own, such as the St. Hughes Hospital, created by the army with the cooperation of the Royal Air Force. This is a large hospital for care of head injuries, under the direction of Brigadier Hugh Cairns and Air Commodore C. P. Symonds.

The Canadians sent to England with their expeditionary force a neurologic hospital equipped for neurology and neurosurgery, along with four general hospitals, now much increased in number. This hospital has been able to centralize the cases of neurologic and neurosurgical conditions from nearby "blitz" activity and the routine casualties of the army and has undertaken the training of representatives from the staffs of the other general hospitals. In Canada no adequate preparation has yet been made to segregate patients with injuries to the nervous system on their return home.

MILITARY PLANNING FOR SPECIAL UNITS

Whatever may be the arrangement of general hospitals in any combat zone, and this must vary enormously, it should be accepted as a general principle that for every five or more general hospitals a neurologic and neurosurgical unit should be planned. These neurologic centers, so far as possible, should care for all the patients with injuries of the nervous system. In addition to the care of their own patients, they should provide for training, for research and for consultation over a wide area. They must cooperate with orthopedic specialists, particularly in the care of injuries of the peripheral nerves.

We have spoken only for neurology and neurosurgery. But the work of Sir Robert Jones,[5] which represents an epoch in medical history, must not be forgotten. The lessons he taught should be heeded and applied to each special branch of medicine.

CONCLUSIONS

Finally, it should be accepted as a principle of organization in military medicine that for every group of general hospitals there should be planned elaborate special units for treatment and consultation and for the teaching of medical officers in each specialty. This paper is intended as a protest and as a warning.

It was in wartime, during the Civil War in fact, that Turner's Lane Hospital began the segregation of military neurologic cases under Weir Mitchell, G. R. Moorhouse and W. W. Keen. The work of these men gave the first impetus to neurology on this continent. If, after eighty years, in spite of the warnings from Cushing, Jones and others, this generation should fail to develop and fully coordinate specialists' units for the care of its military personnel, it may prove unworthy of an honorable professional heritage.

Montreal Neurological Institute.

5. Watson, F.: The Life of Sir Robert Jones, Baltimore, Williams & Wilkins Company, 1934.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

PRIMARY ENDINGS OF THE OPTIC NERVE IN MAN AND IN ANIMALS. OTTO MARBURG, Arch. Ophth. **28**:61 (July) 1942.

Marburg reviews the problem of the primary endings of the optic nerve in man and in animals. The article is well illustrated and has a rich bibliography. The author shows conclusively that the optic nerve appears to be connected with many parts of the diencephalon.

In addition, he makes other significant observations. In spite of earlier claims, he feels certain that antidromic fibers are absent. The existence of a medial optic root in the midbrain of man can be claimed, as in lower-organized animals.

"The nucleus magnocellularis tractuc optici (dorsolateral mesencephalic optic nucleus) in man is a small circumscribed cellular group dorsal and anterior to Fuse's collicular olive.

"The ventral mesencephalic optic nucleus (ganglion ectomammillare), the end station of the basal optic root, is connected with the tectum, into which enter in birds direct and indirect optic fibers of the basal root. In man the dorsal limb of the tractus peduncularis transversus reaches laterally the stratum zonale and the stratum opticum of the anterior colliculus."

Marburg believes that the ventral mesencephalic optic nucleus may be related to the light reflex, a suggestion which he first advanced in 1903, and which more recently was made by Frey, in 1937.

SPAETH, Philadelphia.

A QUANTITATIVE STUDY OF THE PARAVENTRICULAR NUCLEUS AND ITS ALTERATION IN HYPOPHYSECTOMY. H. M. FRYKMAN, Endocrinology **31**:23 (July) 1942.

Quantitative methods were used to determine the number of typical dark cells with prominent peripherally arranged Nissl granules in the paraventicular nucleus of both normal controls and so-called hypophysectomized animals. Twelve animals were operated on, and 14 served as controls. In 9 rats the infundibular process was completely removed, and in 3 some tissue of the posterior lobe was left intact.

A loss of about 35 per cent of characteristic cells of the normal nucleus was observed. In animals with incomplete operations the counts were intermediate. Since the cell loss seems to be caused by a retrograde degeneration following the severing of nerve fibers, it can be assumed that at least 35 per cent of the large characteristic neurons in the paraventricular nucleus send their axons through the infundibular stalk into the posterior lobe of the hypophysis. The lateral wing showed the most prominent loss of typical, dark-staining cells. The light-staining cells within the limits of the paraventricular nucleus apparently show no reaction to resection of the stalk.

Some other factor, such as vascular change, may be responsible for a variation in the relative loss of nerve fibers from the supraoptic and paraventricular nuclei that enter the hypothalamic-hypophysial system.

PALMER, Philadelphia.

THE HUMAN PYRAMIDAL TRACT: IV. A STUDY OF THE MATURE, PYELINATED FIBERS OF THE PYRAMID. A. M. LASSEK, J. Comp. Neurol. **76**:217 (April) 1942.

Lassek studied by means of the Weigert technic medullas obtained from 2 young persons one and a half hours after accidental death. The diameter of 15,000 pyramidal fibers just above the motor decussation was measured in each specimen. An average of 688,000 myelinated fibers was computed. Of the fibers, 89.57 per cent were small, 1 to 4 microns; 8.7 per cent, intermediate, 5 to 10 microns, and 1.73 per cent, large, 11 to 22 microns. About 61 per cent of the area of the pyramidal tract was myelinated. The small fibers occupied about 18 per cent of the area; the medium fibers, 25 per cent, and the large, 18 per cent. There were 55,300 fibers per square millimeter in the pyramid of the specimen from the male and 62,800 fibers per square millimeter in the specimen from the female.

ADDISON, Philadelphia.

THE RELATION BETWEEN EYEBALL SIZE AND THE NUMBER OF OPTIC NERVE FIBERS IN THE DOG. L. B. AREY, S. R. BRUESCH and S. CASTANARES, J. Comp. Neurol. **76**:417 (June) 1942.

The optic nerves of 4 dogs of different breeds were prepared by silver methods and the fibers counted. The total number of fibers ranged from 137,432 to 126,970. Except for 1 animal, there was progressive decrease in the total number of optic nerve fibers with decrease in the weight of the animal. There was a small, but significant, progressive correlation between the size of the eyeball and the size of the retina, on the one hand, and the number of nerve fibers, on the other.

FRASER, Philadelphia.

THE SUPRAOPTIC DECUSSATIONS IN THE CAT AND MONKEY. H. W. MAGOUN and MARY RANSON, J. Comp. Neurol. **76**:435 (June) 1942.

Lesions were made in the brains of cats and monkeys, and fourteen days later the brain stems were removed and prepared with the Marchi technic. Only two supraoptic decussations were differentiated, a dorsal and a ventral. Both bundles originated in the lower part of the brain stem, in part at least, as far back as the pons. The fibers of the dorsal supraoptic decussation pass forward through the medial part of the midbrain and enter the diencephalon in the H field of Forel and ascend in relation to the pallidal bundle. After decussating above and behind the chiasm, they extend laterally and caudally below the entopeduncular nucleus in the cat, or below the medial division of the globus pallidus in the monkey, to enter the lateral part of the internal capsule. The fibers of the ventral supraoptic decussation ascend to the anterior end of the midbrain in the lateral part of the tegmentum, where they pass through the basis pedunculi to run forward on the dorsal surface of the optic tract. They cross within, above and behind the caudal part of the chiasm and extend laterally and caudally on the dorsal surface and in the adjacent portion of the opposite optic tract. Some fibers enter the ventrolateral part of the midbrain and some the medial geniculate body; others reach the rostral, tectal and pretectal regions through the brachium of the superior colliculus. No clear indication of a hypothalamic termination of the supraoptic decussations was encountered.

FRASER, Philadelphia.

PUPILLARY AND OTHER RESPONSES FROM STIMULATION OF THE FRONTAL CORTEX AND BASAL TELENCEPHALON OF THE CAT. ROBERT HODES and H. W. MAGOUN, J. Comp. Neurol. **76**:461 (June) 1942.

Hodes and Magoun stimulated electrically the frontal cortex and underlying parts at successive points by means of the Horsley-Clarke apparatus. Dilatation of the pupils was estimated or measured; activity of the nictitating membrane and respiratory movements were recorded on kymograph paper, and piloerection of the tail was observed directly. In a preliminary operation, section of the cervical portion of the sympathetic trunk was performed bilaterally in 13 animals and unilaterally in 10; in 5 cats one oculomotor nerve was cut, as well as the opposite cervical sympathetic trunk. Serial frozen sections of the brain were studied to check the areas stimulated. The dilator field was chiefly in the gyrus proreus and gyrus genualis of the frontal cortex and extended backward through the basal part of the telencephalon to the hypothalamus. The dilator responses were effected entirely by oculomotor inhibition. The constrictor responses were obtained from the anterior portion of the gyrus cinguli and from the adjacent part of the gyrus genualis and overlapped to some extent the dilator field. Inhibitory effects on respiration were encountered from regions yielding inhibition of oculomotor activity. Piloerection did not occur.

FRASER, Philadelphia.

THE RELATION OF VARIOUS HYPOTHALAMIC LESIONS TO ADIPOSITY IN THE RAT. A. W. HETHERINGTON and S. W. RANSON, J. Comp. Neurol. **76**:475 (June) 1942.

Hetherington and Ranson placed lesions in the hypothalamus of 43 rats by means of a modification of the Horsley-Clarke stereotaxic instrument. A marked degree of adiposity was produced by fairly symmetric lesions which destroyed the medial portion of the hypothalamus, particularly the region of the ventromedial hypothalamic nucleus, or by lesions placed in the caudal part of the hypothalamus in a position to interrupt a large number of the descending nerve fibers from the hypothalamic cell groups. Animals with smaller lesions did not attain as high a level of adiposity as those with larger lesions, nor was the onset of adiposity quite so rapid. Adiposity in the male rats was associated with some degree of

stunting in body length, but this was not true of females. Lesions in the rostral part of the hypothalamus of females often produced a condition of persistent vaginal estrus, as determined by smears, but lesions lying caudal to the infundibulum, which produced pronounced adiposity, did not affect the estrous cycle. There was no significant correlation between the occurrence of adiposity and diabetes insipidus. Histologic examination of the hypophysis revealed that in most of the cases of obesity it was free of scarification.

ADDISON, Philadelphia.

Physiology and Biochemistry

MECHANISM OF ACCOMMODATION. MARTIN P. KOKE, Arch. Ophth. **27**:950 (May) 1942.

The study of the mechanism of accommodation, and the theories connected with it, have for years been in a state of controversy. The Helmholtz theory of accommodation appeared in 1855, and, as Dr. Koke has said, since that time the students of ocular physiology either have been concerned in substantiating his theory or have been equally active in refuting it.

There are two general schools of thought on the mechanism of accommodation. Both agree that the fundamentals of accommodation are contraction of the ciliary muscle and increased convexity of the lens. The followers of Helmholtz believe that the contraction of the ciliary muscle reduces zonular tension, permitting the elastic capsule of the lens to increase the convexity of the lens. The followers of Tscherning believe that the force of the ciliary muscle acting through the zonule and the vitreous forcefully mold a plastic lens into its accommodated form.

The recent theories of accommodation are presented; some seem to substantiate the Helmholtz theory; others tend to disprove it, and some add an entirely new theory based on ocular mechanics quite dissimilar from those already mentioned.

"The differences of opinion on the mechanism of accommodation result because the pieces of the puzzle are lacking which will connect the known but isolated facts to form a definite pattern. The Helmholtz partisans believe that on contraction of the ciliary muscle, the posterior end of the ciliary body and the choroid are pulled forward, allowing the zonule to relax and permitting the lens capsule to shape the lens. On maximal contraction of the ciliary muscle, the diameter of the ciliary corona is so diminished that relaxation of the zonular fibers is too great to be balanced by the elasticity of the lens capsule. Therefore, during the greatest accommodative effort, the lens trembles and sinks with gravity. The longitudinal muscle fibers draw the flat portion of the ciliary body and the choroid forward while the circular fibers pull the ciliary processes toward the lens. The conoid shape of the accommodated lens, shown by catoptric phenomena and evidence provided by eyes frozen while under the influence of physostigmine, results from a corresponding distribution of elastic tissue in the lens capsule.

"The Tscherning disciples . . . conclude that contraction of the radial and the meridional ciliary muscle fibers pulls forward the posterior part of the ciliary body, the choroid and the anterior peripheral portion of the vitreous. The lens periphery is compressed between the anterior capsule, which is being drawn backward by zonular traction, and the posterior capsule, which is pushed forward by the vitreous. The result is increased convexity and the conoid shape of the accommodated lens. The tremulousness of the lens and its tendency to fall with gravity during maximal accommodation were explained by W. H. Luedde. He said that maximal accommodation results in contraction of the circular portion of the ciliary muscle, which releases the lens from the active support of the short suspensory zonular fibers, but the long zonular fibers keep the vitreous compressed against the lens, permitting the lens to tremble with the movement of the eye as would a bead on a mound of jelly. That the lens becomes more spherical when freed of its zonular attachments he explained by the fact that all fluid or semifluid bodies assume a spherical shape when surrounded by uniform pressure."

Experimental work was carried out to determine a new method of observing morphologic changes in the interior of the intact eye during accommodation and to obtain, if possible, information on the mechanism of accommodation insofar as the cat was concerned.

"The method employed was to make cat eyes radiopaque by the intraocular injection of a colloidal suspension of thorium dioxide (thorotrast) and to take roentgenograms of the eyes while they were under the influence of a cyclotonic or a cycloplegic. One-tenth cubic centimeter of the contrast medium was injected into the vitreous with a hypodermic needle inserted through the sclera approximately 8 mm. posterior to the superior limbus. During the injection the point of the needle was observed with an ophthalmoscope. Immediately afterward a paracentesis was done, and 1 drop of 0.2 per cent scopolamine hydrochloride solution was

instilled onto the cornea twice daily for one week. Fragmentation and distribution of the colloidal thorium dioxide were followed by ophthalmoscopic studies and roentgenograms of the cats' heads made at intervals varying from one week to eighteen months after the injection. When the intraocular distribution of the contrast medium was satisfactory, stereoscopic roentgenograms of the isolated but living eye were made. The cat was anesthetized by the intraperitoneal injection of pentobarbital sodium solution (1 grain [0.06 Gm.] per cubic centimeter), 1.3 cc. per 5 pounds (2.3 Kg.) of body weight. A frontotemporal skin and muscle flap was made, and the bones forming the frontal sinus and the lateral and the inferior orbital margins were removed with rongeurs. . . . With the exception of the extraocular muscle cone and its contents, the eye was freed of attachments. Dental films were placed under the eye on the orbital floor and roentgenograms made while the cat's head was fixed and the eye was held in the primary position. The X-ray tube was placed 24 inches (61 cm.) above the eye, and stereoscopic roentgenograms were taken at 15 and at 5 degrees posterior to the plane of the iris and at 10 degrees anterior to that plane.

"Roentgenograms were taken of eyes fifteen minutes after the last corneal instillation of one of the following solutions: (1) 1 per cent physostigmine salicylate, 1 drop, every ten minutes for two hours; (2) 1 per cent physostigmine salicylate and 1 per cent pilocarpine nitrate, 1 drop each, three hours before the roentgenogram and every ten minutes for nine times just preceding it; (3) 1 per cent physostigmine salicylate and 10 per cent mecholyl (acetylbetamethylcholine hydrochloride), 1 drop each, every ten minutes for ninety minutes; (4) 1 per cent physostigmine salicylate, 1 per cent pilocarpine nitrate and 1.5 per cent carbaminoylcholine chloride, 1 drop each, every two hours for ten hours, and (5) 1 per cent atropine sulfate, 1 drop every two hours for ten hours. To compare the interior of an eye under the influence of a cyclotonic with that of the same eye under the influence of a cycloplegic, roentgenograms were made of the eye after instillation of one of the first four medications; then 1 per cent atropine sulfate solution, 2 drops every ten minutes, was given for seventy-five minutes and the roentgenograms repeated. In some cases the atropine was supplemented with 2.3 per cent epinephrine bitartrate solution instilled simultaneously, 1 drop every ten minutes for seventy-five minutes. All the drugs used except the epinephrine bitartrate were in a 1:5,000 zephiran solution, as advanced by O'Brien and Swan for enhancement of corneal penetration. [Zephiran is a mixture of alkyl, dimethyl and benzyl ammonium chlorides. It is a cationic detergent having about the same consistency and physical properties as liquid soap, which is an anionic detergent.]

"The size of the pupil was the criterion of the effect of the drug, the untreated eye acting as a control. In most of the eyes treated with cyclotonics the pupil was a vertical black line at the time the roentgenograms were taken, whereas in the eyes treated with cycloplegics the pupil had a diameter of at least 12 mm. Thirty cats were used; the first 20 were needed in the establishment of the technic. From studies and measurements of the best roentgenograms of the remaining 10 cats, composite stereoscopic drawings of eyes under the influence of cyclotonics and then of cycloplegics were made.

"In order to correlate the details of the roentgenograms with the anatomic distribution of colloidal thorium dioxide, several eyes of which roentgenograms were made were dissected under a microscope immediately after enucleation or after fixation in solution of formaldehyde. The eyes not so examined by roentgenogram were fixed in Zenker's solution, sectioned and studied microscopically."

On the basis of his experimental results, Koke believes that accommodation in the cat's eye is brought about by compression of the posterior periphery of the lens when the tertiary vitreous is forced anteriorly and axialward by the ciliary muscle.

SPAETH, Philadelphia.

EFFECT OF EARLY HYPOPHYSECTOMY ON HYPOTHALAMIC OBESITY. A. W. HETHERINGTON and S. W. RANSON, Endocrinology **31**:30 (July) 1942.

Previous work by the authors has indicated that large, bilateral, symmetric hypothalamic lesions in rats not involving the hypophysis produce extreme obesity. A lesion of this type was produced in a series of rats; 9 of the 10 original animals were then hypophysectomized. In all these animals a high degree of adiposity developed.

Thorough histologic study of the tissues contiguous to the operative site showed that in 6 of the animals hypophysectomy had been complete and in 3 small pieces of pituitary had been retained at the base of the brain. The results are interpreted as indicating that hypothalamic control of fat metabolism and the dysfunction of that control which leads to adiposity do not depend on the hypophysis. Even the presence of this organ may not be essential for the appearance of hypothalamic obesity.

PALMER, Philadelphia.

STUDIES ON THE PHOSPHORUS COMPOUNDS OF BRAIN. S. E. KERR, J. Biol. Chem. **145**:641, 1942.

Dog brain frozen in situ with liquid air contains 19 mg. of acid-soluble purine nucleotide and 2 mg. of nucleoside and free purine nitrogen per hundred grams. Of the nucleotide nitrogen, 83.5 per cent is adenine. Preliminary studies indicate that the remainder is guanine, rather than hypoxanthine. The amount of acid-hydrolyzable phosphorus found attached to the nucleotide is close to that required for full phosphorylation. During autolysis loss of acid-hydrolyzable phosphorus begins within five seconds, reaching a level corresponding to adenosine diphosphate in about three minutes, after which the nucleotide nitrogen slowly decreases to half the normal level within an hour, with a corresponding increase in nucleoside and free purine. No formation of inosinic acid is observed during one hour of autolysis. Adenine, together with hypoxanthine and ribose, is found in the nucleoside-free purine fraction, the adenine decreasing during autolysis. The decomposition of nucleotide to nucleoside and free purine, with a gradual decrease of adenine in the nucleoside fraction and no increase of inosinic acid, suggsts that adenylic acid in brain is first decomposed by a phosphatase, rather than by a deaminase.

PAGE, Indianapolis.

THE OXYGEN CONSUMPTION, CREATINE, AND CHLORIDE CONTENT OF MUSCLES FROM VITAMIN E-DEFICIENT ANIMALS AS INFLUENCED BY FEEDING α-TOCOPHEROL. O. B. HOUCHIN and H. A. MATTILL, J. Biol. Chem. **146**:301, 1942.

Dystrophic muscle from vitamin E–deficient animals as compared with muscle from normal animals has a much higher oxygen consumption, a somewhat lower creatine content and a higher chloride content. Dystrophic hamster muscle showed the most striking increase in oxygen consumption, 250 per cent of the normal. The oxygen consumption rate of paralyzed nursing rats was 160 per cent of normal. Oxygen uptake appeared to increase with the severity of the dystrophic condition. The creatine content was variably decreased, but not greatly, except in slowly developing, severe dystrophy. Oral administration of alpha tocopherol to the dystrophic hamster resulted in the lowering of oxygen consumption toward the normal within twenty-seven hours. The chloride content remained high even after forty-eight hours. Biopsies on the rabbit demonstrated conclusively that alpha tocopherol acetate given by mouth lowered the high initial oxygen consumption of the muscle toward normal, and in as short a time as ten hours. The concentration of creatine was not significantly altered, and the chloride content remained high. Neither the operation nor the anesthesia had any effect on the oxygen consumption or the creatine content of muscle of normal animals.

PAGE, Indianapolis.

TRANSPLANTATION OF MOTOR NERVES AND MUSCLES IN THE FORELIMB OF THE RAT. ROGER W. SPERRY, J. Comp. Neurol. **76**:283 (April) 1942.

In 15 rats the flexor muscles of the elbow joint were transposed to act as extensors; in 7 rats a flexor nerve was crossed into an extensor muscle; in 9 rats one flexor muscle was left intact and another transposed to act as an extensor; in 14 rats two flexor muscles were transposed to extend and one extensor muscle was transposed to flex the elbow; in 10 rats an extensor nerve was crossed into a flexor muscle and another flexor muscle transposed to act as an extensor. All brachial muscles acting on the elbow joint except the test muscles were excised. The rats ranged in age from 15 to 40 days. Active extension of the elbow began to appear at periods varying from seven to nineteen days after operation. After the test muscles recovered function, the contralateral forelimb, the ipsilateral hindfoot and the tail of all but 8 rats were amputated. In most reactions the transposed muscles continued to contract when they would normally have contracted if the muscles had not been transposed. The muscles innervated by nerves of antagonistic muscles continued to contract in the normal action phase of the antagonistic muscles which the nerve had originally supplied. One exception to the resultant reversal of elbow movement was the maintenance of elbow extension during the supporting phases of coordination. This maintenance of extension was dependent on mechanical locking of the elbow joint and on the action of shoulder muscles rather than of test muscles. In spite of amputations and special training, these animals never improved on this adjustment.

ADDISON, Philadelphia.

POSITIONAL NYSTAGMUS IN CEREBELLAR LESIONS. E. A. SPIEGEL and N. P SCALA, J. Neurophysiol. **5**:247, 1942.

After lesions of parts of the cerebellum of cats, particularly the lobus posterior medianus, nystagmus was observed with abnormal positions of the head, particularly when the animal

was in the supine position with the vertex downward. A weak nystagmus with the head in a normal position was increased with abnormal positions, with sometimes a change in its direction, or nystagmus appeared with abnormal positions only. This phenomenon is transient. Electrolytic lesions of the tectal nuclei had a similar effect. In analysis of the receptor mechanism, neck reflexes and retinal reflexes could be excluded. Bilateral labyrinthectomy abolished the effect of position, while a weak spontaneous nystagmus might persist. The authors assume that the appearance of positional nystagmus after cerebellar lesions is a phenomenon of release of parts of the vestibulo-ocular reflex arcs, since it is associated with increase of the experimental postrotatory nystagmus. The experiments suggest that the existence of positional nystagmus should be tested routinely when a cerebellar lesion is suspected.

DRAYER, Philadelphia.

Psychiatry and Psychopathology

"SHAM RAGE" IN MAN. HERMAN WORTIS and WILLIAM S. MAURER, Am. J. Psychiat. **98**:638 (March) 1942.

Wortis and Maurer report 2 cases in the hope of elucidating the problem whether the hypothalamus is concerned with affective expression alone or with affective experience as well.

The first case was that of a young woman, a chronic alcohol addict, who was admitted to the hospital after being in insulin shock for thirty-six hours. After four days of appropriate therapy, she was no longer in coma, but was virtually out of contact with the environment, displayed catatonic tendencies and on stimulation had purposeless, stereotyped, diffuse sympathetic discharges. The authors believe the sham rage resulted from severe cortical damage, so that cortical control over the hypothalamus was removed.

In the second case the patient had attempted suicide by inhalation of gas. When the coma lightened, sensory stimulation produced a sympathetic discharge, again of a diffuse and purposeless nature. Autopsy revealed pronounced vascular and cellular changes in the cortex and the basal ganglia.

Wortis and Maurer conclude that in both cases affective expression was shown but that, especially in the first case, there was no evidence of affective experience.

FORSTER, Boston.

A STUDY OF MANIC-DEPRESSIVE PSYCHOSES OCCURRING DURING THE LATER LIFE PERIOD. EDWIN J. DOTY, Am. J. Psychiat. **98**:645 (March) 1942.

Doty studied 25 patients who after the age of 40 had either their first manic episode or an affective illness characterized by alternating excitement and depression. The average age at admission was 51 for the women and 54 for the men. Ten of them were manic and 10 frankly depressed. Eighteen had somatic preoccupations. Precipitating factors were given for 16 patients. More than one-half the group showed evidence of arteriosclerosis. In a similar proportion the prepsychotic personality was characterized as cheerful, outgoing, active and energetic; about the same number were described as conscientious, sensitive to criticism and highly ethical, and about 15 had overconcern with somatic function. Eighteen of the patients had a positive family history of psychosis. The duration of hospitalization varied from eleven to two hundred and fifty-nine days.

Doty concludes that manic-depressive psychoses are not infrequently manifested for the first time in later life, that therapeutic attention should be directed to the development of a more pliant attitude on the part of the patient and that the prognosis indicates a definite tendency toward chronicity.

FORSTER, Boston.

SCHIZOPHRENIA AMONG PRIMITIVES. N. J. DEMERATH, Am. J. Psychiat. **98**:703 (March) 1942.

Demerath points out that functional disease is no longer considered the special curse of civilized societies and that primitive peoples are now known not to be as simple as they were previously thought to be. However, knowledge of the schizophrenic reaction in primitive societies is inadequate. Ideally, for the investigation of each society the following questions should be answered: 1. What is the nature of the mental disorders? 2. To what extent are the disorders defined in terms of the culture in which they are present, in terms of universal norms and in terms of Euro-American values? 3. Which personality types enjoy the greatest opportunity for expression? 4. What are the adjustment hazards of the abnormal persons? 5. To what extent do psychotic productions reflect interinstitutional and intrainstitutional conflicts? 6. What is the correlation, or lack of correlation, between the development of the civilization and the incidence of mental disorders? This body of material is at present nonexistent.

FORSTER, Boston.

PRESENILE PSYCHOSIS OF THE JAKOB TYPE. GEORGE A. JERVIS, HERMAN HURDUM and FRANCIS J. O'NEILL, Am. J. Psychiat. **99**:101 (July) 1942.

Jervis, Hurdum and O'Neill report the case of a man aged 43 who in the summer of 1940 showed impairment of memory, episodes of confusion and wasting of the muscles of the upper portions of the arms, associated with twitchings. In October 1940 there was slight improvement, but later impairment of judgment and restlessness appeared, requiring hospitalization in January 1941. At that time he was apathetic, euphoric, circumstantial, poor in thought processes and unable to concentrate, retain or recall. The muscles of the upper extremities, shoulders and back were atrophied and weak and showed fibrillations. Pupillary abnormalities were present; gait was unsteady, and speech was slurred. No abnormalities of the spinal fluid could be detected. Slight remissions in the neuropsychiatric status developed, but the general trend was downward. Perseveration, childishness, irritability, weakness of the lower extremities and difficulty in swallowing followed. Death occurred suddenly, one year after the onset.

Gross atrophy of the frontal and temporal lobes was evident, and microscopic examination of these areas revealed thinning of the cortex, with loss of neurons, especially in the deeper cortical layers. The neurons showed various stages of disintegration; the astrocytes were increased in number, and the oligodendrocytes had undergone swelling. No vascular changes could be demonstrated. The parietal and occipital lobes were slightly involved. Similar neuronal changes were observed in the basal ganglia, the medulla and the spinal cord.

Jervis, Hurdum and O'Neill reviewed 24 previously reported cases of this type of presenile disease. The disease is more prevalent in males (3:2), occurs especially in the fourth and fifth decades, has a rapid course, with an average duration of one year, may be divided clinically into three stages and is not infrequently characterized by temporary remissions.

FORSTER, Boston.

THE TOXIC DELIRIOUS REACTIONS OF OLD AGE. G. WILSE ROBINSON JR., Am. J. Psychiat. **99**:110 (July) 1942.

Robinson uses the term toxic-delirious reactions of old age to cover a wide variety of conditions without a common etiologic agent and with a clinical picture varying from collapse to delirious hallucinosis. He observed this disorder in 40 per cent of patients over 60 years of age who were admitted to a mental disease hospital; in half of them this disturbance was the primary illness. The etiologic agents in the cases studied varied from habitual use of drugs to various somatic illnesses. Arteriosclerosis was not considered to play a significant role. The psychiatric material included sleep and behavior disorders, hallucinations, clouding of consciousness and disorientation. Physical symptoms included fever, urinary incontinence, malnutrition, loss of weight and disturbances in the chemical constituents of the blood and urine. The neurologic signs comprised tremors, ataxia, asthenia, incoordination and reflex excitability. From a prognostic viewpoint it is necessary to differentiate the condition from senile psychosis and psychosis with cerebral arteriosclerosis. The differential diagnosis depends on the speed of onset and the circumstances surrounding the development of the illness. Robinson recommends for therapy the intravenous infusion of 10 per cent dextrose and states that since this therapy was instituted the mortality rate has fallen from 13 out of 16 cases to 1 out of 22 cases.

FORSTER, Boston.

FLUCTUATIONS OF BLOOD IODINE IN CYCLIC PSYCHOSES. RUDOLPH NEUSTADT and L. GLADYS HOWARD, Am. J. Psychiat. **99**:130 (July) 1942.

Neustadt and Howard studied the iodine levels of the blood in normal persons and in manic and depressed patients. They found the levels 40 per cent higher in normal subjects than in depressed patients and 40 per cent higher in manic patients than in normal subjects. The changes were found to be correlated with affect, and not with psychomotor activity. Variations in the iodine level of the blood occurred in the same patient simultaneously with changes in the affective picture of the psychosis.

FORSTER, Boston.

MORALE. EDWARD A. STRECKER and KENNETH E. APPEL, Am. J. Psychiat. **99**:159 (Sept.) 1942.

Strecker and Appel compare the systematic, organized propaganda methods of totalitarian government with the comparatively feeble morale-making efforts of our democracy. They state that the development of morale lies within the sphere of psychiatry, since psychiatry is concerned with the mending of personality and morale is the spirit of personality. Moreover, the national personality is the cross section of the personalities of its citizens. Morale has been destroyed in persons who are unable to think about or discuss the war. But more serious

is the systematic undermining of morale by the magnification of a detail, such as racial prejudice, to the point where there occurs obscuration of the main issue, the survival of democracy.

Strecker and Appel point out that morale must be made, and the method for its induction or destruction is propaganda. In its development propaganda should be direct and central. For the destruction of morale counterpropaganda is of little value, whereas anticipatory propaganda is much more advantageous.

Unlike our adversaries and our Russian allies, the French, British and Americans have failed to realize that the previous chief combative factor, the ability to fight, has been enhanced or superseded by a psychologic factor, the will to fight, or morale. The elements of morale are the understanding of the reason for fighting, anger at the enemy, fear of the specific consequences to the individual, willingness to sacrifice and confidence in leaders and self. Morale can be increased by the development of these elements, and psychiatrists are particularly adapted to the development of aggression, fear and morale. The past, present and future of this nation present a wealth of material for truthful propagandizing, and the emotion regarding this material could readily become a driving force. Symbolization is recommended as one method of developing this affective force.

FORSTER, Boston.

COMPARATIVE STUDY OF THE EEGs OF SCHIZOPHRENIC AND MANIC-DEPRESSIVE PATIENTS. PAULINE A. DAVIS, Am. J. Psychiat. **99**:210 (Sept.) 1942.

Davis studied the electroencephalograms of 126 patients with schizophrenia and 81 patients with manic-depressive psychoses. All records were obtained before the institution of drug or shock therapy. In the total group of psychotic patients more abnormalities of the electroencephalogram were observed than in a normal control group. Fifty per cent of the patients with schizophrenia showed fast frequencies, with or without alpha activity. Thirty-six per cent of the patients with manic-depressive psychosis presented predominantly an alpha rhythm. This, Davis concludes, indicates a trend of difference in the patterns for the two psychiatric states. Differences in the alpha frequencies were found, but the differentiation between the brain waves of schizophrenic patients and those of patients with manic-depressive psychoses was primarily in the degree of organization or synchronization of the cortical activity. The common alpha frequencies (10 to 10.5 per second) were less frequent in psychotic patients than in normal subjects. Low voltage records were more prevalent among psychotic patients, but there were no significant differences between the two groups in this respect. The type of activity previously described by Davis as "choppy" was seen in the records of patients who showed schizophrenic deterioration. This activity, the author believes, indicates primarily overstimulation or irritability of the cortex. Similar "choppy" activity can be induced in normal subjects by mezcaline, which at the same time produces symptoms not unlike those of schizophrenia.

FORSTER, Boston.

A PSYCHOSOMATIC STUDY OF ANOREXIA NERVOSA INCLUDING THE USE OF VAGINAL SMEARS. RUTH MOULTON, Psychosom. Med. **4**:62 (Jan.) 1942.

Moulton describes 4 cases of anorexia nervosa which were related in the sense that pregnancy fantasies were dramatized through the functions of eating and menstruating. In 2 cases cyclic vomiting was predominantly premenstrual; in these cases the symptoms appeared to be a hysterical conversion manifestation. The other 2 cases differed in that there were persistent amenorrhea and a persistent phobia for food. The condition in these 2 cases more nearly approximated the diagnostic grouping of anxiety hysteria. Compulsive phenomena were evident in 1 of them. Menstruation, with its associate fantasies of pregnancy, was a threat in all 4 cases and resulted either in a violent action or in repression. The common purposes of starvation were to prevent the onset of menstruation, to prevent pregnancy and to avoid maturity, which would involve the necessity of accepting men and possible marriage. The erotization of eating was evident in the ideas of oral impregnation and oral incorporation of the father's penis. Eating was therefore associated with guilt and anxiety to such an extent that it was avoided entirely in the last 2 cases and was followed by vomiting in the first 2 cases.

The vaginal smear technic of Papanicolaou and Shorr was used by Moulton to investigate the status of ovarian function. The percentage of cornification in the smear was used as an index of estrogen activity. Smears, which were studied for a period of a year in a case of cyclic vomiting, showed that this hysterical symptom was associated with increased cornification. This pattern was interrupted by administration of testosterone and precipitated by estrogen. Menstruation occurred for the first time in two years after suggestion through control injections of sesame oil. A patient with persistent anorexia without vomiting showed

atrophic smears, which improved with a gain in weight. Estrogen induced menstruation but may have increased emotional conflict in this case.

Moulton concludes that therapy of anorexia nervosa is most unsatisfactory. Not one of her 4 patients has remained in good health, although marked improvement occurred. In 3 patients relapses developed after discharge from the hospital. There is no evidence that physical or glandular therapy is helpful. The author favors prolonged psychotherapy in a hospital, especially for adolescent patients, because of the extreme resistance of the parents, as well as the patient.

SCHLEZINGER, Philadelphia.

NARCO-ANALYSIS IN THE TREATMENT OF WAR NEUROSES. J. F. WILDE, Brit. M. J. **2**:4 (July 4) 1942.

Numerous drugs, including the barbiturates, cocaine, hashish, mezcaline, alcohol, barbital sodium and paraldehyde, have been employed to induce narcosis in an effort to facilitate analysis of a patient's mental content. This technic is known as "narcoanalysis." Wilde reports on a series of 50 soldiers suffering from neuroses who were subjected to narcoanalysis, the drug used being pentothal sodium. The method is found to be useful with (1) hysteria, (2) anxiety states, (3) after-effects of injuries to the head and spine, (4) borderline psychoses, mental deficiency and epilepsy when the diagnosis was doubtful and (5) simulation and malingering. The injection is given about two hours after a meal. A 5 per cent solution of pentothal sodium is administered at the rate of 1 cc. per minute, until the patient becomes drowsy or until 10 cc. have been given. Central respiratory paralysis with subsequent circulatory failure, if threatened, should be combated with artificial respiration, inhalations of oxygen and carbon dioxide and the administration of nikethamide or picrotoxin.

Wilde considers the method safe, rapid and sure. He states that the mortality is nil. It is the most rapid method of psychotherapy, with the exception of hypnoanalysis, which requires the services of a skilled hypnotist. It has no after-effects. One disadvantage is that a soldier can refuse this form of treatment, since it is technically an operation.

ECHOLS, New Orleans.

Treatment, Neurosurgery

THE TREATMENT OF CHRONIC ALCOHOLISM. WALTER A. THOMPSON, Am. J. Psychiat. **98**: 846 (May) 1942.

Thompson studied 250 patients hospitalized from six to twelve months because of chronic alcoholism. Men predominated by a ratio of 4:1; the onset usually occurred between the ages of 20 and 35 years; the majority had no psychopathic family background; Irish predominated and nearly 80 per cent had had from one to five admissions. Seventy-two voluntarily joined the "Alcoholic Anonymous" group. Of these, 41 have made an excellent adjustment, although many were among the patients with the gravest prognosis. The author concludes that the movement is an important addition to the treatment of chronic alcoholism.

Thompson believes that the alcohol addict is not hypersensitive to alcohol but that he has a compulsion to drink. The periodic drinker is tense and anxious until he begins an episode of drinking. This is like a similar state in drug addicts. The author concludes that alcoholism is a pathologic habit and is more common than other drug addictions only because alcohol is easier to obtain and use and because drinking is socially acceptable.

FORSTER, Boston.

TREATMENT OF PATIENTS WITH EPILEPSY WITH SODIUM DIPHENYL HYDANTOINATE (PHENYTOIN SODIUM, DILANTIN SODIUM) AND PHENOBARBITAL COMBINED. H. HOUSTON MERRITT and CHARLES BRENNER, J. Nerv. & Ment. Dis. **96**:245 (Sept.) 1942.

Merritt and Brenner report on the treatment of epileptic patients with a combination of phenytoin sodium and phenobarbital. With 100 patients the combined treatment was instituted because of the failure of phenytoin sodium alone. These patients received doses varying from 0.2 to 0.7 Gm. of phenytoin sodium and 0.05 to 0.35 Gm. of phenobarbital per day for from three weeks to thirty-one months. Thirty-four per cent of the patients were moderately or greatly improved, while the remaining 66 per cent showed no significant improvement. The latter group included all patients with exclusively petit mal, psychomotor or jacksonian seizures. For 37 patients who had not previously received phenytoin sodium the results of the combined treatment corresponded fairly well with those reported

by Merritt and Putnam for phenytoin sodium alone. The authors conclude that if phenytoin sodium alone, in adequate dosage, fails to control a patient's seizures, a combination of phenytoin sodium and phenobarbital, each in full dosage, should be tried.

CHODOFF, Langley Field, Va.

THE ELECTRICAL SHOCK TREATMENT OF PSYCHOSES. WILLIAM FURST and JOHN F. STOUFFER, J. Nerv. & Ment. Dis. **96**:499 (Nov.) 1942.

Furst and Stouffer report their results with the use of electric shock therapy of the schizophrenic and affective psychoses. Complications of treatment included vertebral fractures, a fracture of the acetabulum, dislocations of the jaw, status epilepticus (1 case), cardiac arrhythmias and activation of pulmonary tuberculosis (1 case). Seventy-three per cent of the patients with affective reactions experienced remissions sufficient to permit discharge after an average stay in the hospital of forty-five days, while 24 per cent of the schizophrenic patients were discharged after an average period of hospitalization of three months.

CHODOFF, Langley Field, Va.

A SUGGESTED TREATMENT OF SPINAL BLOCK CAUSED BY SPINAL ADHESIVE ARACHNOIDITIS BY MEANS OF REPEATED SPINAL AIR INJECTION. HOWARD D. MCINTYRE, J. Nerv. & Ment. Dis. **96**:668 (Dec.) 1942.

Adhesions between the arachnoid and the pia and dura of the spinal cord may cause partial or complete subarachnoid block. Such adhesions vary from fine bands to dense sleeves and may form cystlike structures. The cause is often obscure, but the adhesions may form as a result of a meningeal reaction in gonorrhea, syphilis, typhoid, influenza, encephalitis, bacterial meningitis or virus infections. McIntyre describes 4 cases, in all of which there were complete spinal block, a yellow discoloration and marked increase in protein in the spinal fluid. In 3 of the cases treatment was by laminectomy, with indifferent results. In a fourth case repeated injections of 30 cc. of air were made into the subarachnoid space. By this method manometric block was relieved, followed by considerable improvement in the neurologic picture. The author suggests that this method be tried before laminectomy is considered.

CHODOFF, Langley Field, Va.

ON THE USE OF CURARE IN MODIFYING CONVULSIVE SHOCK. LAWRENCE F. WOOLLEY, JACK R. JARVIS and G. S. INGALLS, J. Nerv. & Ment. Dis. **96**:680 (Dec.) 1942.

Woolley, Jarvis and Ingalls report their experience with shock therapy modified by preliminary curarization. The patients selected had chronic, serious illnesses which had not yielded to any other form of therapy. The authors emphasize the inadvisability of treating young persons with schizophrenia since their recovery is about the same rate without shock treatments. Of 38 patients treated with curare and metrazol or curare and electric shock or both, 8 have recovered to their prepsychotic level, 7 are on a parole status, 4 are slightly improved and 19 are unimproved or worse.

Curare was administered intravenously in the form of intocostrin in the approximate dose of 1.1 mg. per kilogram of body weight. Within ninety seconds evidence of muscular weakness appeared, and the maximum effect was present in one hundred and fifty to two hundred and ten seconds. Shock effects should be concentrated as much as possible between the second and the fifth minute after the administration of curare. The effect of curare in raising the convulsive dose of metrazol was slight. No fracture of the long bones or of the vertebrae occurred in any of the curarized patients. Among the hazards introduced by curare were difficulty in breathing, due to weakness of the muscles of the tongue, neck and thoracic cage, accumulation of mucus in the throat, and stridor due to laryngeal or bronchial spasm. In general, the blood pressure and the heart action were not seriously affected by curare, and the authors conclude that, in proper dosage and with proper administration, the drug is safe to use.

CHODOFF, Langley Field, Va.

FRONTAL LOBOTOMY IN THE TREATMENT OF CHRONIC PSYCHOTIC OVERACTIVITY. L. H. COHEN, R. G. NOVICK and A. ETTLESON, Psychosom. Med. **4**:96 (Jan.) 1942.

The authors report on the results of frontal lobotomy in 6 patients whose psychoses were characterized by persistent aggressiveness, destructiveness and excitement. All the patients were probably schizophrenic and had been ill for periods varying from eight to twenty-eight years. An observation period of one year had elapsed since operation. Some degree of "improvement" is claimed in 5 of the 6 cases. By improvement is meant reduction in the over-

activity so that a more satisfactory adjustment in the ward was possible. In none of the cases was any neurologic complication observed. The authors conclude that the efficacy of frontal lobotomy in the treatment of chronic psychotic overactivity must still remain in doubt. However, the operative procedure seems to produce sufficient benefit to warrant further study of such otherwise hopeless psychotic patients.

SCHLEZINGER, Philadelphia.

d-DESOXYEPHEDRINE. A. C. IVY and F. R. GOETZL, War Med. **3**:60 (Jan.) 1943.

Ivy and Goetzl present a complete review of the literature on the action of *d*-desoxyephedrine hydrochloride. [The product most frequently used in Germany is pervitin.] In man and animals the action of this drug is similar to that of amphetamine sulfate, but it is more potent per milligram. In doses of 3 to 6 mg. it is said to be preferable to amphetamine sulfate because it is more likely to produce elevation of mood, willingness to exert oneself to the utmost, decrease in the sense of fatigue and a counteraction to feelings of boredom and sleepiness, without undesirable effects. As the data on experiments which compare the action of the two drugs in man are few, it is conjectural whether this claim, put forward by the Germans, is true.

Although the German authors state that the drug is not habit forming, it has been placed under the German narcotic prescription law.

PEARSON, Philadelphia.

CONVULSION THERAPY OF MALIGNANT NEUROSES. J. TITECA, Confinia neurol. **5**:37, 1942.

Titeca has made use of shock therapy in certain cases of grave neurosis, with excellent results. He reports 6 cases of professional or war shock, with various sensory and motor manifestations of a hysterical nature; in some of the cases there had been resistance to all types of therapy for years. The author believes that convulsion therapy has no value as a means of suggestion in the treatment of hysterical states. He asserts that modifications in the cellular metabolism, as well as changes in the cortical cells which accompany the convulsive crisis, are of therapeutic import.

DEJONG, Ann Arbor, Mich.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

GEORGE A. BLAKESLEE, M.D., *President, New York Neurological Society, in the Chair*

Joint Meeting, Dec. 8, 1942

Use of Focused Ultrasound Waves to Produce Transcranial Focal Lesions of the Brain: A Preliminary Report. DR. JOHN G. LYNN and DR. TRACY J. PUTNAM.

The subject of this presentation is the more recent use of focused ultrasound waves (Lynn, J. G.; Zwemer, R. L., and Chick, A. L.: The Biological Application of Focused Ultrasonic Waves, *Science* **96**:119-120, 1942. Lynn, J. G.; Zwemer, R. L.; Chick, A. L., and Miller, A. E.: A New Method for the Generation and Use of Focused Ultrasound in Experimental Biology, *J. Gen. Physiol.* **26**:179-193, 1942) to produce transvertebral and transcranial focal lesions of the nervous system in animals. To date, however, such local neural lesions have always been associated with severe necrosis of the adjacent area of the scalp or skin lying in the path of the ultrasound radiations, although there was no detectable damage to the bone or the meniniges. Hence one finds oneself in the same uncomfortable and unenviable position as the early users of high voltage roentgen therapy. Despite their early success in the treatment of deep-lying tumors, these workers had still to perfect methods of preventing severe cutaneous burns by reducing the surface absorption of the radiations. Similarly, with focused ultrasound radiation there is still much work to be done in determination of the optimum frequency, intensity, time of exposure, etc., which is necessary before one can expect to minimize or eliminate surface injury and so produce purely focal effects. Yet, despite the complicating surface damage, sufficiently circumscribed focal changes and lesions in the brain have been produced by transcranial transmission to justify this early report.

Greutzmacher (*Zentralbl. f. Physiol.* **96**:342, 1935) first developed in his physics laboratory the curved quartz plate method of focusing ultrasound waves, but, so far as we know, our studies represent the first biologic application of this method of obtaining enormous local concentrations of ultrasonic energy. We have used a frequency of 835 kilocycles, which gives a focal point as small as the wavelength, namely, 1.8 mm. in diameter.

Experimental Results (slides and motion picture demonstrations).—The production of lesions in vitro was achieved by use of blocks of fresh liver tissue obtained from recently killed animals. The many cellular interfaces of the tissue absorb a large amount of the ultrasonic energy, and a short exposure at a high intensity was required to drive the radiations at the frequency employed through the tissues to produce a purely focal damage, with negligible effect on intervening hepatic tissue.

The production of in vivo lesions of the brain and cord of living animals is made still more difficult by the additional factor of circulating blood, which absorbs and disperses some of the radiations. However, despite these increased difficulties, well localized lesions of the brain and cord were produced through the skull and vertebral column, in association with injury and necrosis of the overlying soft tissues.

In all, 3 dogs, 30 cats and 4 monkeys were used. The usual exposure was ten to fifteen minutes, with the animal under ether anesthesia. Some of the disabilities produced were contralateral monoparesis, from irradiation of the opposite cortical motor area; blindness following the bilateral irradiation of the occipital cortex, and ipsilateral incoordinations and ataxia following application of the radiation to one cerebellar hemisphere.

In illustration of the results obtained with the 37 animals used, motion pictures of 2 animals, a cat and a monkey are shown. The cat was first given a ten minute dose at maximum intensity over the upper lumbar region of the vertebral column, without any apparent effect other than the production of a superficial burn and edema of the underlying soft tissues. On the theory that these soft tissues were thick enough to absorb the radiations before they reached the cord, the skin and the posterior vertebral muscles, together with several spinal processes in the upper lumbar region, were removed. The region of the exposed vertebral column was then given the usual ultrasonic irradiation of ten minutes at maximum intensity.

The animal exhibited complete bilateral paralysis of both hindlegs, with loss of all sensation in this region. Five days after ultrasonic wave treatment the animal showed partial recovery of motor function and sensation, but still exhibited a severe degree of bilateral paresis of the hindlegs. At this time he was killed by intracardiac injection of a 30 per cent concentration of solution of formaldehyde U. S. P., and the brain and cord were removed, fixed, sectioned and stained.

The monkey, like the cat, was under ether anesthesia. However, only the hair was shaved from the scalp before exposure to the radiations. An effort was made to damage the left cerebral motor and premotor arm areas only. This was successful, and several hours afterward the monkey exhibited typical spastic paralysis of the right upper extremity. Ten days later there remained well defined residual paresis of this member. At this time the animal was killed and examined, and its brain was photographed, fixed, sectioned and stained.

Pathologic Observations.—In the cat there was edema of all the tissues in the path of the beam. This was most intense in the more delicate tissue elements, such as the myelin, the axis-cylinders and the nerve cells, and slight demyelination was produced. Autopsy revealed a slight reaction of the glia.

In the monkey the damage was far more intense and localized, and a definite line of demarcation had become established. The area of damage was in a state of coagulation necrosis, affecting all tissue elements. The outlines of cells were vaguely visible, but their staining properties were lost. This area of necrosis showed no liquefaction and was practically uniform throughout. The zone of reaction around the necrotic area showed typical mesodermal repair, and capillaries were beginning to sprout into the area. Outside this zone of reaction was a zone of damage to ectodermal structures, resembling that seen about a softening of comparable size. The acute lesion was limited to the cortex. The subjacent white matter showed changes resembling those seen in the cat, which may, however, have been in part secondary.

DISCUSSION

Dr. Harold G. Wolff: From time to time investigators pursue the design of an instrument that will produce a lesion deep in the structure of the brain without leaving a path through which the damage is done. Often the complexity of the apparatus and the ingenuity of the arrangements have exhausted the creative drive of the operator, so that when an instrument has been devised investigation ends. What promised to be a contribution to a study of function of the nervous system turns out to be only a new device. Perhaps the most successful apparatus of this type is Hess's modification of the Horsley-Clarke apparatus. By its means Hess was able to injure small areas in and around the third ventricle and so shed light on the problem of sleep. Dr. Lynn and Dr. Putnam have presented a kind of interval report, a report of progress. They have brought to the attention of the society an apparatus which is said to produce a lesion deep in the nervous system without evidence of too much destruction between the deep lesion and the cortex. Apparatus in the hands of Dr. Putnam has always yielded much in the past. One recalls that innocent apparatus for determining the seizure threshold which produced phenytoin, and one can look forward with interest and enthusiasm to a similarly fruitful result from this device. However, at the moment the apparatus is still in the phase of development.

Dr. Charles Davison: Dr. Lynn and Dr. Putnam have used an ingenious method for the application of focused ultrasound energy in the production of lesions in the central nervous system. This experiment is significant, for the pathologic changes, although more severe in their animals, somewhat resemble neural lesions caused by detonations of highly explosive bombs, blows on the back producing abnormal straightening of the spine (as in automobile accidents), the sudden stopping of a fast moving train, or caisson disease. As is well known, with many such accidents there may be temporary or permanent loss of neural function. Frequently the neurologic signs may be found in regions distant from the original point of the blow; this is especially true of the spinal cord. With these types of injuries, in addition to petechial hemorrhages, there may be small areas of necrosis distal to the point of the blow. Claude and Lhermitte and others have described cases in which such areas of necrosis followed shell explosions. The blow, in these instances, was not received directly by the patient, and the vertebral bodies usually remained intact. I observed similar areas of necrosis in a case of injury to the spinal cord in which the patient was thrown out of an automobile, without evidence of injury or fracture of the vertebrae. Mairet and Durante reported medullary concussions in animals induced by vibrations of the air following the detonation of high explosives. Guillain maintained that in a number of his cases concussion was due to changes in air pressure produced by the force of the explosion. It seems that the mechanical vibrations produced by the ultrasound method are somewhat similar to the vibrations of the air following the detonation of high explosives.

Of further interest is the compensability of the neurologic signs produced in the animals. This sort of reversibility has also been noticed in man after trauma to the skull or spine. Is it possible that the focused ultrasound waves led to vasospasm of the vessels in the affected regions? I wonder whether Dr. Lynn and Dr. Putnam succeeded in demonstrating vasopasm in their specimens.

The fact that there were demonstrable lesions in the central nervous system without evidence of neurologic signs does not surprise me. As demonstrated by the authors, the myelin was more extensively involved than the axis-cylinders. Apparently, there was some restoration in the function of the axis-cylinders.

Dr. Putnam and Dr. Lynn showed that when ultrasound waves are directed to the brain there is a tendency for the damage to be directed to the cortex, that all tissue elements are destroyed by a sort of coagulation necrosis and that the vascular stroma shows relative resistance to the damage. I judge that this effect depends on the intensity of the ultrasound waves, for, as seen with application of powerful high voltage roentgen rays, the vessels are also injured. Frequently one notices, in addition to the sprouting capillaries, excessive endothelial proliferation of the vessels.

Dr. Foster Kennedy: For some half-dozen years I have believed that by ultrasound vibrations it should be possible to stop the transmission of impulses across the bundle of His and that this could be used as a weapon of war. I see no reason that this should not be done. It may seem inappropriate in a medical meeting to suggest that what Dr. Putnam has demonstrated as a physiologic experiment should be turned into a weapon of death. But I am certain that it could be done. I wrote to Adrian two years ago asking that physiologists apply their minds not simply to individual therapeutics, but to mass destruction. I am sure results would follow.

Dr. Tracy J. Putnam: As Dr. Wolff has pointed out, this investigation is to be classified as an experiment in apparatus rather than as an addition to the therapeutic armamentarium. This apparatus, obviously, is not a practical device at present, and it probably never will be. It would be regrettable, however, if there were no attempt to utilize in the solution of medical problems the newer technical methods which electrical and mechanical technology affords. It is just possible that there may be a further modification of this apparatus which will make it practical for use in the operating room, as diathermy now is, or in the physiologic laboratory.

To turn to the pathologic changes, it seems to me entirely reasonable that the lesions produced should be similar to those caused by the impact of high explosives. The lesions produced by mechanical impacts which I have seen consist of softenings following closure of vessels, and I have the impression that the blast phenomena are also largely of the same type. The lesions in these experiments are not, on the whole, of this type. They represent, rather, mass destruction of the tissue, the vessels as well as the other elements, within the zone of destruction, so that the area is almost like a caseous focus, with traces of the original structure left behind. The nearest parallel I know is that of an electric burn, in which a high tension current has passed through the skin and reduced it to a kind of tanned leather without producing liquefaction.

Dr. John G. Lynn: If I allowed my wishful thinkiing to run away with me, I would be inclined, like Dr. Kennedy, to speculate on the possibilities of focused ultrasound energy as an instrument of destruction in war. As a matter of fact, I had such ideas some years ago, but after learning a good deal more about the properties of elastic or mechanical radiations, particularly about one characteristic of high frequency ultrasound waves, I was forced to abandon the idea. The characteristic property I speak of is the fact that with frequencies above 200,000 cycles the vibrations are transmissible with difficulty through gases of any kind, although they penetrate liquids and solids with much less absorption. I am afraid, therefore, that one will have to give up the idea of making such waves a war weapon, because one cannot get the Nazis or the Japs under the water or under the ground; if they were there, they would not need any ultrasound waves to finish them off.

Dr. Foster Kennedy: They go under the water with submarines.

Dr. John G. Lynn: You are perfectly right. The French scientist Langevin (Sound Transmitters for Under-Water Signalling, British patent no. 145691, 1920), before the last war, was a pioneer in the use of ultrasound waves for the purposes of secret underwater communications. He found that secret intervessel signaling could be achieved through projecting a narrow beam of ultrasound waves under water, like a flashlight beam, so that it could not be picked up by the enemy, but could be detected only by the ship at the receiving end of the beam. The battle of Jutland was nearly won by the German navy partly because the

German ships, by this secret and efficient method of communication, knew what each vessel was to do and how well it did it, without the British being able to discover or pick up their means of intercommunication. The British were still using easily intercepted wireless signals. Now all navies use the ultrasound beam for underwater intership signaling, as well as for detection of submarines and depth soundings. It cannot be used as a weapon in the air. In fact, even in laboratory experiments, if there are a few bubbles of air, instead of oil, between the diaphragm of the generator and the head of the experimental animal, the ultrasonic radiations are absorbed and prevented from penetrating the tissues. One has to have some liquid or solid substance as a transmission medium.

DR. RICHARD BRICKNER: What about using these waves to destroy submarines?

DR. JOHN G. LYNN: That might be possible, for they can be transmitted as a narrow beam through water, but it would taken an enormous amount of power at a much lower frequency than we have used.

Nature and Incidence of Acute Emotional Disturbances in Torpedoed Seamen of the Merchant Marine Who Are Continuing at Sea. DR. SYDNEY MARGOLIN (by invitation), DR. LAWRENCE S. KUBIE, DR. MARK KANZER (by invitation) and DR. LEO STONE.

Through the cooperation of the National Maritime Union, facilities and the opportunity were provided for the study of seamen of the Merchant Marine who had been torpedoed. Forty men of a group who had indicated their willingness to return to sea submitted themselves. Detailed information on the psychiatric status of each subject was obtained and analyzed in terms of the severity of the reaction in correlation with the past personal history and with circumstances connected with the torpedoing.

Because of the limited number of subjects and the special conditions of sampling, all conclusions must be looked on as merely suggestive. The interval between the time of the torpedoing and the examination ranged from three weeks to two years, the period for the majority being two to three months.

1. Of the men examined, 25 per cent had severe persisting reactions; 50 per cent had mild to moderate persisting reactions, and 25 per cent had no persisting reactions.

2. Pathologic alcoholism (addiction with or without "horrors") or a history of a previous psychiatric illness apparently predisposed to severe reactions.

3. These pretraumatic factors and consequent extreme reactions occurred with the highest frequency among the Anglo-Saxon and Scandinavian members of the steward's department. The lowest incidence occurred among the Negroes and Latin-Americans. The latter racial groups are under considerable sociopolitical pressure to enter the steward's department, and, unlike the white workers in this division, their presence there did not represent a free choice determined solely by endogenous factors.

4. Among the white men showing severe reactions the following pertinent circumstances existed: They were predominantly from the steward's department. All had marked alcoholism, and one-half presented pathologic alcoholism. One-half these men gave a history of previous mental disease. Examination of one-half the subjects yielded evidence of latent or overt homosexuality or of sexual inhibition. The Negroes and Latin-Americans presented no severe alcoholism, and only 1 was suspected of having had a previous mental disorder. One-half were married, and there were no evidence of sexual irregularities.

These data are presented not as etiologic factors but as circumstances about which inquiries can be easily made, and in this way they may assist in the selection of stable men for the Merchant Marine.

As a group, the men were consistently friendly and willing, and even eager, to talk about themselves. Many had the traditional "hard-boiled" exterior, but intellectual interests were common, despite limited school attainments. The majority had gone to sea before the age of 18, usually in the course of a strong, inarticulate need to get away from home and from disciplined social authority and regimentation. This rebelliousness, together with deep gratification derived from the life at sea, was apparently so intense that, despite the presence of severe reactions, many of the men experienced a lessening of anxiety and of other symptoms when they returned to the real dangers of sea.

While political, social and economic attitudes among the men were widely divergent, they were intent on service in the war effort and had a sense of loyalty to and pride in their union.

On the basis of the data obtained from the detailed histories and from discussions with authorities on Merchant Marine problems, a series of specific recommendations were made.

These were concerned primarily with methods for the selection of merchant seamen and methods of training them to meet disaster effectively and to render mutual aid to one another, and with the emergency psychiatric care of rescued survivors.

DISCUSSION

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Another important factor in regard to this study is that whereas the men of the armed forces, the Navy and the Army, have certain privileges under the government pension laws, the men of the Merchant Marine have not. Personally, I hope they never get such privileges, for at present men suffering from traumatic neurosis in the Merchant Marine do not have a "compensation neurosis" on top of that. The result is a pure culture of the traumatic neurosis, and that will be of help in evaluating the results of treatment and the etiologic factors and in starting a program of prevention, which we now have in mind.

As the cases reported by Dr. Kubie have brought out, I have a deep conviction that traumatic neuroses develop after the men have been through a great deal of hardship but that the condition usually occurs as a direct result of some personal element that has come into the situation. A man has been at odds with the skipper, has had some trouble with a friend or has not heard from home for a long time; the last factor applies particularly to Englishmen, who go for long periods without news from home. I suggest that the personal element is something to which one should pay considerable attention in seeking the causation of the neurosis. I believe that as long as his morale is good a man will be unlikely to have a traumatic neurosis.

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The correlations which Dr. Kubie has discussed, such as the severity of the traumatic experience, the age of the seaman, the length of sea service and the nationality, are, I suppose, considered on the basis of what would logically be expected to have some relation to the pathologic reaction, but in this, as in other fields of psychiatry, it is not usually the obvious that is the effective agent in producing a neurosis. As a matter of fact, if I did not know Dr. Kubie so well, I should suspect him of being naive; knowing him, I am sure he discussed these correlations just to demonstrate that they do not have much significance. Of course, the number of cases is rather small; yet I am inclined to believe that if it were ten times as large there would be essentially the same negative correlation. This is, of course, just

another way of stating what Dr. Blain said in closing, that it is the introduction of the element of personal relationship somewhere along the line that is particularly important. It was only two or three days ago that one of the seamen was telling me that his ship was regarded by all the men aboard as unseaworthy, while the captain was rather indifferent and disinterested; the ship was dirty and vermin infested, and it seemed to me that all those factors tended to reduce his morale and sense of security and prepared the way for his traumatic neurosis.

I should like to comment on the general level of American seamen. I knew nothing of this group previously; as a matter of fact, I had the same impression that many people probably have, that they are rather uncultured, uncouth and hard boiled. However, I must say, and I should like to emphasize this, they are not what they are popularly thought to be. Rather, they are cultured; they have a very real self respect, and the neurosis, in part, represents a loss of this self respect, often with associated guilt feelings.

The question of why they go to sea is also interesting. The full story, which has not yet been told, is that many go to sea to escape conflicts over the feeling of being rejected. It is interesting that these men seem to find their sense of security in a ship and the sea, and in the particular kind of close personal association which they find at sea. This, again, may have something to do with the development of neuroses in some of them. Here, the particular place and situation in which they have found their security lets them down, so to speak; it blows up on them, actually as well as figuratively. The experience is psychologically traumatic depending on what the man reads into it or how he regards it in relation to himself. I do not believe that the severity of the traumatic experience has much to do with the neurosis. Again, it sometimes appears to be not so much the traumatic experience as what happens afterward that is important. In some of these men the neurosis has apparently not developed until they are back "on the beach," as they say—until they have returned to shore.

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order to show the subtlety of the feelings which these wholly unschooled men were able to make articulate. To work with them was one of the most illuminating experiences I have ever had.

DR. FOSTER KENNEDY: Dr. Kubie said that the torpedoed seamen were asked to come to his office, which was, I remember, just beside the welfare office. The seamen who came were the seamen who were examined. The same thing was done in England, at all the ports; less than 6 per cent of the torpedoed seamen ever went to see a physician. Therefore the men who went to see a physician were the men who were ill. They are not to be considered at all as representative of the hundreds who have been torpedoed. It is an unscientific procedure to take less than 6 per cent, as though they were representative of 100 per cent; further, I should like to protest against the idea that every man who goes to sea must be in some way psychopathic.

DR. LAWRENCE S. KUBIE: I cannot let that comment go without correcting what might be a serious misapprehension. In the first place, Dr. Kennedy did not listen carefully. I said explicitly that the men were sent to us by the dispatchers and by the union officials for only one reason, namely, that they had been torpedoed or bombed and were shipping back to sea. Not one man came to us seeking treatment. We said: "Do not select men who have been giving you trouble; send us the run of the mill." Any man who had been through a torpedoing was a candidate. A less selected sampling of the total group could not be made. Our conclusions, therefore, are limited as to their validity only because the group is small. Forty cases prove nothing. I should not be surprised if with a larger group the percentage of neuroses were to drop somewhat, but I doubt whether it would drop far. The 6 per cent which Dr. Kennedy mentions is wishful thinking on the part of some one.

As to whether all seamen are psychopathic, we are likely to get into an argument. The term "psychopathic" means something definite to me, and it does not mean a seaman. On the other hand, I am quite certain that there are deeply buried unconscious forces which explain why the large majority of these men left home and went to sea before the age of 18, from families who had no sea tradition.

The Role of Instinct in Human Behavior. DR. JUDAH MARMOR.

Probably no other single concept in modern psychologic thought has been so subject to misuse as has that of "instinct." In large measure, the confusion which exists has been due to the failure to distinguish clearly between a biologic need (e. g., hunger, thirst, sex), its presumed aim (e. g., reproduction, hunting, self preservation), its motor pattern (e. g., walking, running, grasping) and its emotional concomitants (e. g., fear, anger, sympathy). The result has been a hodge-podge of terms loosely used, in which almost every observable human reaction has at one time or other been characterized as instinctive.

Most scientific definitions of instinct in recent times conceive of it as an inherited complex pattern of behavior, entirely automatic and unlearned, and comprising within its inherited scope the cause of an activity, its goal, the behavior necessary to consummate it and its emotional concomitant, if any. The most perfect examples of such patterns are observed in insects. Similarly, much of the behavior of animals has been considered phylogenetically predetermined, and not requiring any learning process. It was by analogy with these observations, and under the evolutionary influence of Darwin, that Freud, in common with other psychologists of his time, was led to approach the problem of human behavior from the standpoint of its phylogenetic, biologic roots and to postulate theories of human behavior based on the concept of instinct.

In the past forty years, however, there gradually has been accumulating a growing body of facts which casts serious doubt on the validity of the entire concept of instinct and questions its applicability in particular to the behavior of higher mammals and of man. Experimental studies on insects, fish, birds, lower mammals and infrahuman primates indicate that as the evolutionary scale is ascended, more and more of the patterns of behavior which have been assumed to be native or instinctive are in reality learned, adaptive reactions.

The reasons for this are inherent in the neural structure of the organism. The lower the animal form, the more completely developed is its neural structure at birth and the more totally is it equipped to cope with its environment. This also means, however, that the capacity for plasticity and variability of behavior is extremely limited. The higher the animal form, on the other hand, the more helpless is the infant, and the less fully developed at birth is its neural structure. This means that the completion of the process of myelination and the development of sensory-motor executive functions are effected in relation to environmental influences. The result is a notable broadening of the plasticity and possibilities of adaptation of the organism. That these environmental influences in early infancy are a pre-

requisite to the development of the full functional capacity of the human brain is clearly illustrated by the permanent mental retardation which results in isolated children whose brains have completed their myelination in the absence of social influences. In other words, the vast range and complexity of modern human behavior are dependent not only on the inheritance of a human brain and body, but, equally important, on that vast social inheritance which is called culture. Without it, as in the instance of isolated children, the son of a civilized man becomes nearer to the beast in his behavior than to his own father.

It becomes clear, then, that to speak of "human nature" as some form of human behavior, thought or emotion which is determined by purely biologic or inherited factors, and would exist even in a state of isolation, is erroneous. There can be no "human" nature apart from some form of human society, and the character of that "nature" will inevitably reflect the character of that society. This formulation does not in any way deny the existence of certain basic biologic drives or needs which man shares in common with all other animals—needs for food, water, sexual gratification and protection from the elements. But the aims which these drives take in human beings, and the objects toward which they are expressed, can be understood only in terms of the specific social relationships to which the human being has been exposed.

Similarly, the old conflicts of heredity versus environment, or biology versus culture, become meaningless when viewed from the organismic approach of modern psychology. The organism is immersed in an environment from the very beginning of the life cycle. Each stage of development is determined by the cooperation of hereditary and environmental forces. Since the earlier stages influence the character of the development of the later stages, the hereditary and environmental factors interpenetrate more and more as development proceeds. Nowhere is this more true than with human beings, in whom the cultural factors become indissolubly interrelated with organic processes through the laying down of language patterns in the association centers of the cortex. There thus develops a new unity which is qualitatively unique in the animal world—a sociobiologic unity—which is called human nature. This interpenetration of the biologic and the cultural influences is so complex and so complete that one cannot separate the hereditary from the environmental factors without destroying the specific quality which constitutes the nature of man, just as one cannot separate water into hydrogen and oxygen without destroying that quality which constitutes water.

The fact of major importance which emerges from all this is that there is no such entity as a fixed, immutable, universal "human nature." Since the nature of man depends equally on his biologic and on his social inheritances, significant changes in either sphere may alter it. On the recognition of this fact rests the conviction and hope that out of the titanic world struggle which is now going on there will emerge a better world in which to live, where the potentialities of man may be raised to ever greater heights of creativeness and self fulfilment.

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DISCUSSION

DR. ISRAEL S. WECHSLER: Dr. Marmor has presented in lucid language the problem of instinct and has touched on a number of fundamental points. Actually, it is extremely difficult to define scientifically the word instinct. Unfortunately, most authors have used it in its literary, rather than in its scientific, sense. Obviously, from the literary point of view one can have no quarrel with the loose use of the word. To say that one has the instinct of a gentleman is absurd from the scientific standpoint, yet permissible and understandable. Unfortunately, most psychologists use the word just as loosely as do literary men and delude themselves into thinking that they are scientific. There is a delusion abroad that to define a word anew, to coin a novel phrase or to add a literary nuance is to create a scientific fact. This is a serious mistake, made worse by the fact that good writing so often conceals bad thinking. In passing, I should like to take exception to the use of the word "instinctual." Webster defines it as "pertaining to instinct." Here, again, the conversion of a noun into an adjective only adds to confusion.

Perhaps the best use of the word instinct in its biologic sense is in respect to reflex patterns, which may be simple or extremely integrated and complex. Some of these reflex patterns are established early; others become integrated only as growth and development proceed. As with intelligence, so with instinctive behavior; one cannot distinguish between what is primary and what is secondary, what is innate and what is acquired. Frequently it is difficult to distinguish between instinctive behavior and intelligent behavior. One of the best definitions of intelligence (Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, Williams & Wilkins Company, 1939, page 3) is: "The aggregate or global capacity of the individual to act purposefully, to think rationally, and to deal effectively with his environment." If one limits the definition for the moment to purposeful action and effective dealing with environment,

one finds that one cannot distinguish between instinctive and intelligent behavior. Certainly, animals from the highest to the lowest act purposefully and effectively. This is why so many animal lovers insist that animals act intelligently.

Another difficulty in the use of the word is its teleologic connotation. It has frequently been pointed out that teleology is a religious, and not a scientific, concept. Ultimate purposes are substituted for primary causes. Without quarreling with the religious use of the doctrine, one must point out that it is pseudoscientific and merely serves to confuse that which it pretends to clarify.

It seems to me that one should limit the use of the word instinct to simple and integrated reflexes. Sucking, which is commonly given as an example of the earliest reflex pattern, is observed, together with grasping, as a decerebrate rigidity phenomenon. One observes that, as the infant learns to seize the nipple for sucking, it also learns to grasp the breast.

As with intelligence, so with instinct, one cannot dissociate the primary reflex phenomenon from the complex integration which comes with learning. Just as one cannot say with finality where native intelligence ends and learning begins, so one cannot say where "pure," or "innate," instinct ends and complex integration begins. To repeat, I doubt whether in the present stage of knowledge the word instinct has a well defined place in science. If the scientist wishes to use the concept, it seems to me better to limit it to primary, innate, acquired or integrated reflexes, at various levels of the nervous system, from the lowest to the very highest. As to the literary use of the word instinct, one need have no quarrel with it provided one knows that one is not scientific. In any case, I am glad that Dr. Marmor has again called attention to the loose employment of the word and to its frequent misuse.

Dr. Abraham Kardiner: Dr. Marmor's paper touches a complicated subject. I can, therefore, use my time to best advantage in amplifying some of the obscure points. His paper touches on two separate themes: The first is the relation of the biologic to the psychologic use of the term instinct. The biologist uses the concept in a descriptive sense; it is a convenient term to describe certain phenomena from a behavioristic point of view. Much evidence has accumulated to show that biologists were a bit hasty about the innate character of the "instinctive" reactions, because such responses prove, on close examination, to be influenced by experience, discrimination and choice. Such discoveries, however, do not destroy the descriptive value of the concept of instinct. The biologist can, therefore, use the concept with impunity and is responsible to no working procedure or theoretic structure as a consequence.

The situation is quite different with the psychologic use of the term. Here the concept of instinct may be employed not in a descriptive sense—that is, to indicate the existence of certain phenomena—but in an operational one. In the latter sense the concept is used as a ground plan for a systematic theoretic structure, and here the psychologic concept, in contrast to the biologic, carries a load of responsibility. This is the manner in which the concept has been used in psychoanalysis and in MacDougall's psychology, and this is the aspect that is challenged when one questions its operational value. Many psychoanalysts regard such a challenge as a denial of the validity of Freud's work or of drives in general. This is far from being true. The challenge merely states that theoretic formulations in terms of instinct may be inaccurate and may omit a large number of phenomena which cannot be included in a formulation which accepts the instinct or drive as the phenomenon to which the explanation is polarized.

One might gather the impression from Dr. Marmor's paper that the situation with respect to the vicissitudes of the concept of instinct in psychoanalysis is unique. On the contrary, this difficulty exists in every contemporary school of psychology. They all have trouble with the notational systems employed and the basic units used for explanatory purposes. The *Gestalt* as a basic unit leads to one kind of difficulty, and the conditioned reflex leads to another, as latter day behaviorists are discovering to their chagrin. So crucial has this problem become that one psychology has made it its avowed purpose to devise a fool-proof notational system, namely, topology, which can be used in any psychology. The success of this attempt is questionable. To my knowledge, no psychology today denies the existence of drives, but not all of them make the drive the central phenomenon to be used in the explanation. This is a point that can be settled only experimentally.

The reason that such difficulties arise, in any psychology, is that this collection of disciplines does not have at its disposal a universal language which has the precision of mathematics, with fixed and invariable meanings. One is obliged to use the concepts of common sense, which are incapable of the precision which the data demand. Whereas those who try to devise more precise psychologic tools have an obligation to prove their case, it is at least an equal obligation to listen to the evidence. Alteration of operational tools does no violence to facts; they concern only the interpretation and use of these facts. Moreover, new operational tools often lead to the discovery of new phenomena.

A second point in Dr. Marmor's paper is that the particular assumptions in connection with the concept of instinct in psychoanalysis have been prejudicial to a proper appreciation of the role the social environment plays in shaping the human nature one is attempting to study. This is quite true, and the accumulating evidence is decisive. This question can be answered only in the laboratory of comparative social psychology, and not by waging word battles as to whether biologic or sociologic factors are more important. Wherever man is found, he is the product of a given set of social conditions acting on his biologically determined makeup. It is not a question of "either . . . or," not a question of how much influence each exerts, but one of simultaneously continuous interrelatedness. The fact that man is a creature of learned, and not predetermined, reaction types does not invalidate the concept of drives; it only qualifies the varying vicissitudes and emphases to which these drives are exposed in different social settings. The specific human nature observed is, therefore, always a function of the specific institutional emphases and stresses exerted on the biologic makeup of man. When the subject is studied experimentally, by way of comparative anthropology, strange variations come to light. For example, among the Alorese of the Netherland East Indies the women show little tenderness, except sporadically, toward their children. As compared with maternal care in our own society, their protective and normative functions are distinctly poor. Can one assume, therefore, that the maternal instinct or drive is feeble? Such variations in inherited endowment would frustrate any attempt at a systematic social psychology. Moreover, in this case one need postulate no such far-fetched hypothesis; the absence of interest can be accounted for on more immediate grounds. First, the dependency cravings of these women are frustrated in early and late childhood. For a few years between late childhood and puberty they are inducted into feminine pursuits without adequate rewards. Often at this time they are pressed into the maternal role and obliged to take care of younger siblings. Having enjoyed little maternal care themselves, they undertake this role reluctantly. By the age of 15 they marry. It is no wonder that they have little interest in or aptitude for the maternal role, and their gardening duties keep them occupied all day. A similar situation exists for the men, among whom strong attachments to the father are rare. However, there are exceptions. Thus, 1 man among 4 whose biographies were studied had a strong attachment to his father, who was a forceful and good parent. This man had a typically strong superego, passive homosexual attitudes and inhibitions toward women. The other 3 who had poor parental care had a low superego formation, a deep sense of isolation, inhibitions toward women, but no evidence of strong parental attachments. In this illustration the exception proves the rule, for in those cases in which parental care was adequate the child responded in a normal manner. This case also shows that the variations lie not in the inherited endowment but in the adaptive integrational systems which are built around specific needs common to all children of any race. A systematic study of this kind can go a long way toward solving the problem of the relation of biologic equipment in a social milieu. Such a work I shall, with the aid of several collaborators, shortly publish.

DR. GREGORY ZILBOORG: I think that every one will agree that had Dr. Marmor had more time his paper would have appeared even more brilliant, and, with Dr. Wechsler, that his beautiful writing would then have concealed even better a good deal of bad thinking.

First of all, nothing is more easy in fields that touch general concepts in science than to build up a concept and then destroy it. If one were to follow literally what Dr. Marmor said, one would conclude that man is what the Augustinian philosophers thought him to be sixteen centuries ago, a *tabula rasa,* that he has a definite biologic status but that psychologically one can make anything of him. It is interesting that those who stress culture and social environment forget that these factors also have their origin and that it is not an accident that man functions through cultural agencies. Fifty years ago Lester F. Ward, an entomologist, who was also a great sociologist, said there was no inherent similarity, psychologic or sociologic, between the social reactions of animals and those of man.

What interests me is that Freud, who apparently was patted on the back tonight, and also kicked, never spoke of "instincts" in terms of medieval concepts. He did not speak of the maternal instinct, of the instinct of loving, of the instinct of quarreling or of the instinct of grasping and sucking. Freud was as far from the medieval psychology of instincts (faculty psychology) as the critics of Freud are far from understanding him. Both Dr. Marmor and Dr. Kubie spoke of drives, and those who are interested in scientific terminology ought to be aware that the word "instinct" does not exist in the German language and that Freud always used the word *Trieb,* which is to be translated as "drive," not "instinct." When one speaks of a monkey who can be taught to do certain things and use the trial and error method, one should not call this an instinct of trying and erring; it is a drive. The fundamental drives are biologic. One will have to return to the medieval concept of man as a passive machine

which can receive learning, and as an active machine which can learn, and overlook the fact that man has changed very little in the past two thousand years, either in his heredity or in his way of looking at life and at his fellowman. On the basis of Dr. Marmor's concept, one can deny the biologic basis of the maternal instinct, for in Tahiti there were groups organized for the purpose of sexual orgies, and a prerequisite for joining these groups was an oath that no children should be born in this community, and that any baby born had to be killed by its own mother. The mothers killed the babies as soon as they were born.

Freud never spoke of the maternal or the paternal instinct, may I repeat—he spoke of drives. To borrow the word instinct and make it into a straw man and then destroy the straw man does not get at the root of the problem. The problem is extremely simple, and I, too, would approach it from the sociologic point of view. In this overdeveloped, highly centralized society, where the struggle for existence is immense, there is always a great mass of diffuse anxiety, and because of this and the increase in insecurity, there is only one thing for a man to do—like the man whom Dr. Kubie studied, who suddenly thought of himself as God and who, when he came out of danger, thought of himself as a physician. When a man is at his lowest psychologic ebb, he enters the highest state of euphoria and becomes megalomanic. Through a study of comparative sociology, one finds that in great crises man always develops a megalomania, which expresses itself in an overemphasis of his fantasied will to master the world. One may say, then, that man is teachable and learnable and can be transformed into anything one desires. Man creates, then, a philosophy of mastery of his own fate and makes culture and society its adjuncts. Man has never saved himself from stark realities in this manner, and he has failed to improve himself through mere fantasy, for he has remained a victim of his own drives.

Dr. Lawrence S. Kubie: Despite the lateness of the hour, I want to pour oil on these troubled waters if I can. First, a controversy over instinct versus culture has as little scientific validity as the old bubbling controversy over heredity versus environment. If either side states its position carefully, and listens carefully to the argument of the presumptive other side, it quickly finds that it has no opponent. One can fight on this issue only by assuming that one has an opponent who takes an indefensible extreme position opposite one's own. In the literature one finds two kinds of statements: careful definitions of position, with which no one can quarrel, and inflammatory, controversial statements, with which no one can agree. I repeat that no one who thinks carefully, and who formulates his position without ire, can find any one to disagree with in this whole matter. As an issue, it has been used chiefly to allow people who don't like each other to throw stones at each other.

An example of this is Dr. Marmor's definition of an instinct. It is one which he himself does not accept for any of the higher animal forms. Nor does any one else. Either one must say that there is nothing instinctual in the life of man, or else one must modify ones criterion of an instinct. Dr. Marmor's criterion of an instinct is not merely that it must have a hereditary origin, but that the entire pattern of behavior must be determined solely by innate hereditary influences. In "instinctive" acts he will allow to the learning processes no power to modify the hereditary nucleus. If such modification occurs, according to his criterion, the behavior is no longer instinctive. No experimental biologist could concur in this.

Last year two colloquia were held at the New York Psychoanalytic Institute, each lasting two full days and devoted entirely to the elucidation of this problem. Participating in these colloquia were psychologists, biologists, experimental physiologists, anthropologists and psychiatrists. Its proceedings have appeared in the April and October 1942 issues of *Psychosomatic Medicine,* pages 166 and 390. In the end a formulation was arrived at which got rid of this entire controversy. The essence of instinctive activity, the thing which distinguishes it from a reflex, is the source of the energy which drives it. Instinctual behavior depends on recurrent biochemical tides in the body, which create tensions which must be discharged or gratified. Obviously, in this respect the instinctive activity differs from the knee jerk or any other simple reflex. Instinctual behavior, then, is behavior which arises out of tensions which have been created by one of the basic spontaneous physiologic tides of the body. The form of activity which discharges the tension may be wholly inherited in lower forms, but in higher species only the kernel of the pattern is hereditary, and this may be infinitely modified by the learning processes and by the subtleties of conditioning reflexes.

This does not make it any less necessary to recognize that there is a group of activities the roots of which are instinctual in this sense. And this is the essence of the freudian concept of the role of instincts, *Trieb* or drive in human life. It is the gasoline which drives the automobile, rather than the steering apparatus. With this concept it is impossible for any thinking psychologist or psychiatrist to disagree.

On the other hand, Freud also evolved a theory of a sequential evolution of human drives (or "instincts"). In this theoretic concept the development of the infant is described as consisting of a sequence of epochs, in each of which one area or aperture of the body occupies for a short time a dominating position in the psychologic status and in the behavior of the infant. Freud speculated further that the influence of any event would vary, depending on the particular phase through which the infant was passing at the time of the event, and that a person can become psychologically arrested at one phase or another.

These theories have been useful working hypotheses in clinical work. They have been valuable in guidance of the careful observation of developing infants. Yet no one can say that these concepts have been wholly proved or wholly disproved. Like any other scientific hypothesis, they must be tested piece by piece, and not a ray of light is thrown on this important field of experimentation by heated and confused controversy about "instinct versus culture." All too often this discussion has been used merely as a means of letting off steam either for psychoanalysis or against it, or, more subtly, in the interests of a particular theoretic approach to economic and political problems.

That Dr. Marmor is justified in criticizing the careless expansion of the concept of instincts cannot be questioned. I am quite sure, however, that if he were to stick to a restricted, antiquated and outworn definition of instincts, he would find himself confronted by forms of human behavior for which he would have to invent some new term. He would then find that he meant by this term precisely what most mean in speaking of "instincts."

DR. JUDAH MARMOR: I seem to have sown the wind and reaped the whirlwind! I regret that for lack of time I must omit discussion of Dr. Wechsler's and Dr. Kardiner's comments, other than to express my appreciation.

Dr. Zilboorg is a difficult person to debate with, because in his own modest way he is himself a master of rhetoric and presents his point of view so brilliantly. I should like, however, to correct a few of the fallacies which he has expressed. One is that I have presented the mind of a man as a *tabula rasa,* on which anything can be written, depending only on the particular culture in which that mind develops. This is a misrepresentation of what I have said. I do not deny that man has certain biologic limits, that he has a human brain and body and that his development must be within the limitations of these biologic structures. Moreover, I conceive of man not as a purely passive structure, mechanically reflecting his environment, but as an active dynamism with definite innate drives, which, however, from the very beginning of development are significantly molded and influenced by interreactions with the environment. What I am arguing against is a conception of man which regards his biologic nature and his cultural patterns as two fundamentally separate phenomena which are merely superimposed one on the other. The cultural reactions, according to Zilboorg, are merely superimposed on the biologic ones, and in moments of stress, presto, the cultural ones fade away, and the unadulterated "biologic nature of man," with all its "native" aggressions and passions, comes to the fore. This is a mechanistic view, which I have endeavored to contradict. The concept I have presented tonight is a dialectic one; it holds that the biologic and cultural factors are so intimately fused in the developmental history of man that the two can never thereafter be completely separated.

Another point which Dr. Zilboorg has raised is one on which Dr. Kubie also touched, namely, that Freud's use of the concept of *Trieb* signified biologic drive, rather than instinct. Is it not curious that in translation this word has always been interpreted as "instinct," rather than as "drive"? I think there is a reason for this—Freud actually used the term to connote something very similar to the concept of instinct, and something comprising within its scope not merely the biologic drive but a fixed developmental pattern, and in some instances a fixed goal also. I see Dr. Zilboorg shaking his head, but the facts speak for themselves. For example, in Freud's concept of the libido, he presents a picture of a phylogenetically predetermined pathway which the sexual drive must inevitably follow—an oral phase, an anal phase and a genital phase, preceded by a phallic phase. There one has not merely a biologic drive, but a drive with a fixed developmental pattern, which Freud believed existed in all societies, in all cultures and in all men. Consider further the freudian concept of the Oedipus complex. There Freud postulated a more or less fixed and inherited aim or goal for the sexual drives of the child, a goal which, again, he conceived as occurring in all cultures and in all men. The researches of modern anthropologists amply contradict this assumption.

As to Dr. Kubie's insistence that he uses the word instinct only in the sense of a biologic drive or tension, I cannot but feel that this is a misuse of the word which can only lead, as it already has, to confusion in the long run. If by instinct psychiatrists refer simply to physiologic drives or tensions, why not use the latter terms? The result is bound to be a clarification of formulations and sounder theory and practice.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding*

Regular Meeting, Dec. 10, 1942

Follow-Up Study of Lead Poisoning in Infants. DR. RANDOLPH K. BYERS and DR. ELIZABETH LORD.

A follow-up study of 20 children who had been discharged from the Children's Hospital as cured of lead poisoning is presented. The diagnosis of lead poisoning at the time of the original admission was made in conformity with standards suggested by various authors. In addition, all the children had roentgenographic evidence, either consistent with or characteristic of lead poisoning. At the time of their primary hospitalization, 9 of the children were thought to present no evidence of involvement of the nervous system by lead; 3 showed peripheral neuritis, and the remaining 8 had encephalopathy, usually in a very mild degree. All were infants when they were first seen, and all but 1 obtained the lead by chewing painted objects. All the children were discharged from the hospital as recovered. Developmental data obtained at the time of their original admission strongly supported the presumption that they were of average intelligence.

When they were observed after entrance to school only 1 of the 20 children was progressing normally. In 5 children general intellectual deficit, as shown by intelligence quotients between 65 and 85, seemed to account for the failure to learn. The remaining unsuccessful children exhibited sensorimotor defects, and these seemed to account for their failure to grasp the fundamental school technics of reading, writing and arithmetic. When examined late in infancy, this group was less able than average babies of their age to manipulate blocks, put pegs and forms in appropriately shaped holes in boards or scribble with a crayon. Their social and language development was much nearer the average. Later, ability to copy designs and reproduce them from memory was impaired. Such defects in many instances greatly retarded, and in others appeared to have blocked, the acquisition of writing, reading and spelling. Sensorimotor defects of this nature have been studied by a number of observers, all of whom agree that they are evidence of injury to the cerebral cortex.

In addition, other signs of injury to the nervous system occurred. In 3 of the children recurrent convulsions developed. In a few instances scattered neurologic signs, such as clonus and the Babinski phenomenon, appeared for the first time during middle and late childhood.

Disturbances in behavior were common. The children were of the impulsive type, their behavior stemming from lack of judgment and self control. Three of the children had been permanently excluded from school for such behavior. Many observers have correlated activity of this sort with injury to the brain by various agents.

All but 1 of the 20 children who had had lead poisoning in infancy showed defects of cerebral function in childhood. Lead poisoning occurring early in life tends to interfere with the normal processes of growth and development of the cortex.

DISCUSSION

DR. BRONSON CROTHERS: These children represent the more favorable fraction who made progress after lead poisoning. The difficulties of appraisal were great but were, I believe, surmounted. Obviously, efforts were made to determine the rate of growth before the lead was ingested. Then psychologic prediction was attempted. The progress was charted against this prediction. Dr. Lord and Dr. Byers convinced the rest of us at the hospital that the conclusions offered were based on valid procedures.

It is obvious that lead poisoning in children is rarely recognized and that its effects are disastrous. Since it is a completely preventable disease, further study is abundantly justified.

DR. AUGUSTUS S. ROSE: Does Dr. Byers believe that the development of the neurologic signs after the original poisoning was due to chronic lead poisoning, or do these signs become evident as the child grows older? I should also like to know whether there is any information on the exact mechanism by which lead causes disturbance in the function of the nerve cells. That is, does lead act as a poison to the nerve, or does it in some way deprive the nerve of an essential substance?

DR. RANDOLPH K. BYERS: To answer the first question, I believe that the appearance of neurologic signs must be related to chronic poisoning. I cannot prove it, but such children obviously contain lead in their systems and excrete it for long periods.

As to the effect of lead poisoning on nerve tissue, not much is known, except in cases of the acute form. The pathologic characteristic is swelling of the nerve cells themselves—not of the myelin—but the change is not specific for lead. So far as I know, it could be produced by any one of a number of agents.

DR. G. COLKET CANER: I should like to ask more about the neurologic changes observed. Do the neuritic symptoms ever develop some time after the absorption of the lead? Is it possible for the children to carry the lead in their systems for a long period before symptoms develop?

The authors spoke of having noted the Babinski sign. Were any other abnormal signs observed? They referred to "sensory and motor changes." I should like to know why they used these terms. Did the children not show difficulty in memory?

DR. RANDOLPH K. BYERS: The neurologic changes were mostly with respect to the motor signs. We did not make examinations for sensibility to heat, cold, etc. Some children who had severe lead encephalopathy, with considerable cerebral edema at the time of hospitalization, and whom we did not follow in this study, showed, for example, pronounced hemiplegia.

I do not know whether the "sensorimotor" changes were all sensory or all motor. The children showed inability to organize movements of the hands in relation to what they knew perfectly well. Some of the difficulties were best shown, perhaps, in the 7 to 8 year old children, who would look at a diagram and then, in trying to copy it, could not make their hands draw the last line. They seemed to know that the movements were wrong, but could not get their hands to move in the proper direction. As some of the children grew more capable and the defect became less, they would finally fumble into organizing the movements of their hands.

DR. G. COLKET CANER: Could such disability be defective revisualization?

DR. RANDOLPH K. BYERS: No, not usually. The condition has something to do with memory and ability to organize abstractions, which did not have much meaning for them.

DR. H. HOUSTON MERRITT: What has the law done about lead paint? Is not its use forbidden in the manufacture of cribs and toys?

DR. RANDOLPH K. BYERS: This is voluntary with the manufacturer. Many of the parents of these children stated that they had repainted the crib, which had become battered. Most of the children's furniture, or perhaps all that comes from reputable dealers, is painted with non-lead-containing paint, and that is true of toys. It is not true, however, of painted window sills and porches.

DR. H. HOUSTON MERRITT: How is the lead finally eliminated from the system?

DR. RANDOLPH K. BYERS: It is probably excreted slowly, over a long period. We do not try to delead the tissues. Active attempts to do so were made in a few cases, and most of the children became very sick when we mobilized the lead so that it could be excreted in sufficiently large quantities.

DR. PAUL B. JOSSMANN: In connection with convulsions, especially jacksonian convulsions, I should like to know whether electroencephalographic studies were made which may have demonstrated the presence of a focus, perhaps in a portion of the cortex.

The behavior pattern of the children suffering from lead encephalopathy seems to me similar to that of children with epidemic encephalitis. I should like to know whether Dr. Byers' observations revealed the same thing.

DR. RANDOLPH K. BYERS: The convulsions of the 3 children in this particular study were generalized. One had diffuse changes in the electroencephalogram, that is, changes over the entire cortex, with large, slow waves and no particular focus. One had one-sided attacks, not jacksonian, and with lead poisoning it certainly is possible to have localization restricted more to one side of the brain than to the other. I think this type of behavior came from diffuse damage to the cortex, and probably is not specific to any one disease.

Diagnosis and Surgical Treatment of Intractable Exophthalmos. DR. JAMES L. POPPEN.

The many causes of exophthalmos, both bilateral and unilateral, are discussed in detail, with emphasis on the fact that acquaintance with the differential diagnosis is important, so that an orderly investigation of the etiologic factors can be conducted and, as soon as the diagnosis has been made, advice as to treatment and probable prognosis given. An outline of

the causative factors and number of cases (87) with which I have had personal experience in the last ten years (1933-1943) follows.

Cause	No. of Cases
Systemic disease	
Diseases of the thyroid	28
Hypertension	5
Syphilis	1*
Leukemia	1
Angioneurotic edema	0
Prolonged use of thyroid in treatment of obesity	2
Pyemia resulting in orbital abscess	1†
Paget's disease	2
Intracranial pressure (causing pressure erosion of orbital plates)	
Tumor of brain	4
So-called increased intracranial pressure without tumor	2
Congenital defects	
Encephalocele	0
Aneurysm	1
Arteriovenous (orbital varicosity), internal carotid and ophthalmic artery	1
Cranial synosteosis	2
Orbital tumors	
Meningioma of sphenoid wing (hyperostosing)	11
Schüller-Christian disease	0
Osteoma	3
Cholesteatoma	3
Carcinoma	
Metastatic	2
Primary in nasal sinus	1
Sarcoma	
Osteogenic	1
Neurogenic	1
Rhabdomyosarcoma	0
Angioma	
Arterial	1
Venous	1
Lymphangioma	0
Glioma of optic nerve	2
Neurofibroma	1
Mucocele	1
Pseudotumor	1
Mixed tumor of lacrimal gland	1
Lipoma	0
Fibroma	0
Infections	
Osteomyelitis	
Pyogenic	1
Tuberculous	1
Syphilitic	1
Thrombosis of cavernous sinus	2
Orbital abscess	1
Infection of lacrimal gland	1
Trauma	
Hematoma of orbital tissues	1

* Same case as that of syphilitic osteomyelitis.

† Same case as that of pyogenic osteomyelitis.

Orbital decompression was advised only in the cases of advanced progressive exophthalmos in which danger to eyesight or loss of the eyeball was imminent. The present technic of

orbital decompression (Naffziger's operation) is described. No operative mortality was experienced in 29 cases, although 1 patient in whom adequate decompression could not be carried out because of extension of ethmoid cells into the orbital plate died as a result of the malignant exophthalmos one year after operation.

DISCUSSION

DR. DAVID G. COGAN: I have little to add from the neurologic point of view. In nearly all cases of extreme exophthalmos the condition develops after a thyroidectomy. It has been the hope of my associates and myself that we would have some way to distinguish before the operation on the thyroid the patients in whom the malignant type is likely to develop and those in whom it is not. I do not think that any reliable criteria are available at present. However, one thing is worth mentioning. A normal eye may be pushed back into the orbit 2 to 3 mm. by pressure on the lid. Similarly, the eye with the usual protruding of exophthalmic goiter may be made to regress with pressure, but with the malignant type of exophthalmos pressure on the eye encounters considerable resistance. It is as though one were pushing against so much putty. I hope that this difference in compressibility will be a useful means of distinguishing the good prospect from the bad one before operation. There is a further distinction. Patients with the malignant type complain of diplopia or give evidence of involvement of the extraocular muscles early.

DR. GILBERT HORRAX: There is no question that Dr. Naffziger made a great step in advance by devising this method of orbital decompression. I hope that some way will be discovered by which operations can be avoided, as they are tedious. However, if two surgeons work together it is much easier.

As to the ability to tell in which patients exophthalmos will develop after thyroidectomy, what will one do about it even if one can distinguish? However, any possible help in this respect will be of value. Dr. Poppen has been modest about his own part in this procedure; after all, surgery is made up of many tricks, and Dr. Poppen has modified the operation a good deal himself. For instance, there are certain ways of cutting down the amount of bone work that has to be done on the outside, as well as other devices which have made the operation easier and the results better.

DR. MADELAINE R. BROWN: I wonder if Dr. Cogan was at the medical ward rounds at the Massachusetts General Hospital two weeks ago, when 2 patients were pointed out who had been treated with strong solution of iodine U. S. P. and of whom it has been predicted that they would have progressive exophthalmos. I am not sure that the exophthalmos had regressed, but it had not progressed. Apparently, if cases of this disease can be detected in the beginning, the condition can be controlled with medication, rather than surgically.

DR. GILBERT HORRAX: Can this condition be controlled permanently with strong solution of iodine U. S. P.? I know it can temporarily.

DR. MADELAINE R. BROWN: The results were thought to be satisfactory.

DR. DAVID G. COGAN: I have seen a few patients, not more than 10, with the malignant type of exophthalmos. The impression that I have obtained from the thyroid clinic is that such patients are amenable to treatment with strong solution of iodine U. S. P. and thyroid. The patients to whom Dr. Brown refers had, as I recall, a very low metabolic rate and had been treated medically for some time.

I should like to mention 1 case of particular interest, since the condition came on after self administration of thyroid for obesity. After the patient had taken 3 grains (0.195 Gm.) a day for about a year, symptoms of thyrotoxicosis developed. She stopped taking the thyroid, and her nervousness cleared up, but the exophthalmos increased. Examination showed the typical malignant type, with involvement of the extraocular muscles and putty-like resistance of the eyeball to pressure.

In Dr. Poppen's 2 cases which followed treatment of obesity with thyroid was the exophthalmos of the malignant type?

DR. JAMES L. POPPEN: No, the exophthalmos in these cases was not progressive. The patient in whom the exophthalmic goiter developed had to have an operation later, but when thyroid medication was stopped with the other the condition remained the same or improved. Yes, I agree that the degree of resistance of the orbital tissue can be determined by pressure on the eyeball, and this resistance is one of the most important factors in determining the degree of involvement of the retro-orbital tissues. One does not have to worry much about the patient with prominent exophthalmos and little resistance of the retro-orbital tissues to digital pressure on the eyeball, whereas the patient whose orbital tissues offer firm resistance to pressure on the eyeball must be watched carefully. With respect to the conservative measures, Hertz, Means and Naffziger (as a matter of fact, the work was started in Naffziger's

clinic) observed that if thyroidectomy was done, with rapidly progressive exophthalmos and fulminating thyrotoxicosis, malignant exophthalmos was likely to follow. However, Naffziger has changed his mind about that, I believe, and some of the patients under my observation have had roentgen treatment for thyrotoxicosis, with a ten year history of exophthalmos, and malignant exophthalmos has then developed.

With regard to the efficacy of strong solution of iodine, I thought that 1 of the patients of Hertz and Means would be better off with a Naffziger operation. With the continuation of strong solution of iodine U. S. P. and some thyroid, it is true that the patient's condition has remained approximately the same as before and has not become fulminating. I still feel that several factors should be taken into consideration in deciding on the necessity of orbital decompression. Certainly, a beautiful young woman with disfiguring exophthalmos or a person in public life should be given the benefit of any doubt, especially since the mortality is negligible.

DR. AUGUSTUS S. ROSE: After the orbital plate is removed, does intracranial pressure increase?

DR. JAMES L. POPPEN:: My associates and I do not measure the intracranial pressure routinely, so I should not answer one way or the other. I think perhaps the pressure is increased for a few days, because one does manipulate the frontal lobes. These patients displayed some disorientation. We assume that manipulation of the frontal lobes results in postoperative edema.

DR. H. HOUSTON MERRITT: Is the pituitary ever irradiated in treatment of this disease?

DR. JAMES L. POPPEN: Yes, but it does no good.

DR. AUGUSTUS S. ROSE: In the photograph I noticed the bags under the eyes. What is the cause?

DR. JAMES L. POPPEN: It is due to edema of the fatty tissue.

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, Jan. 21, 1943

Cervical Syringomyelia and Syringomyelia-Like States Associated with the Arnold-Chiari Deformity and Platybasia. DR. BEN W. LICHTENSTEIN.

This paper was published in full in the June 1943 issue of the ARCHIVES, page 881.

Mechanisms of Headache. DR. HAROLD G. WOLFF.

Pain-Sensitive Structures of the Head.—The sensitivity to pain of the tissues covering the cranium, the cranium itself and most of the intracranial structures has been ascertained from a series of patients during surgical procedures on the head. Some of the "pain pathways" and the mechanisms of headache are defined.

The use of a variety of stimuli has resulted in the following conclusions about the sensitivity to pain of the structures investigated:

1. Of the tissues covering the cranium, all were more or less sensitive to pain, the arteries being especially so.

2. Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain, the fifth, ninth and tenth cranial nerves and the upper three cervical nerves were sensitive to pain.

3. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses were not sensitive to pain.

Except for the sensations that resulted from stimulation of the parenchyma and cranial nerves, the only sensation that was experienced on stimulation of the intracranial structures was pain. Stimulation of the pain-sensitive intracranial structures on or above the superior surface of the tentorium cerebelli resulted in pain in various regions in front of a line drawn vertically from the ears across the top of the head. The pathways for this pain are contained in the fifth cranial nerve. Stimulation of the pain-sensitive intracranial structures on or

below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and in the upper three cervical nerves.

From the data available, six basic mechanisms of headache from intracranial sources have been formulated. Headache may result from (1) traction on the veins that pass to the venous sinuses from the surface of the brain and from displacement of the great venous sinuses; (2) traction on the middle meningeal arteries; (3) traction on the large arteries at the base of the brain and their main branches; (4) distention and dilatation of intracranial arteries; (5) inflammation in or about any of the pain-sensitive structures of the head, and (6) direct pressure by tumors on the cranial and cervical nerves containing pain afferent fibers from the head.

Intracranial disease commonly causes headache through more than one of these mechanisms and by involvement of more than one pain-sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly responsible for headache.

Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain-sensitive structures. However, disease of remotely separated pain-sensitive structures may cause pain and hyperalgesia in identical areas. Pain referred to the head from disease of tissue not in the head does not occur, with the rare exception of pain in the jaw or the neck associated with angina pectoris. Sepsis or fever of any organ may be associated with headache, but this is not referred pain.

Headache Associated with Changes in Intracranial Pressure.—The headache so frequently associated with abnormally high or low cerebrospinal fluid pressure has long been the subject of contradictory speculations. In a study of headache associated with changes in intracranial pressure, relevant factors were analyzed. In normal human subjects, headache was induced by drainage of cerebrospinal fluid through a lumbar needle. Then studies of headache and spinal manometrics made while the subject was shifted on a tilt table gave the following results: Headache was regularly induced in erect human subjects by the free drainage of approximately 20 cc. of cerebrospinal fluid (about 1 per cent of the total intracraniospinal contents), the estimated vertex pressure falling to between —220 and —290 mm. of fluid from a normal of approximately —130 mm.

Drainage headache was reduced in intensity by the intrathecal injection of saline solution and restoration of the volume of cerebrospinal fluid. It could also be reduced in intensity by tilting the body toward the horizontal, or simply by flexion or extension of the head. In its response to postural changes, drainage headache was shown to be independent of the estimated intracranial pressure. On the other hand, drainage headache was usually increased in intensity during distention of the intracranial veins secondary to bilateral jugular compression. The afferent impulses from the frontal portion of the area of drainage headache traverse chiefly the fifth cranial nerve.

It is thus inferred that drainage headache is caused primarily by traction by the brain on various pain-sensitive structures which anchor it to the cranium; dilatation of some of these structures, the intracranial veins, and increase in brain volume are suggested as joint factors in the augmented traction which follows drainage of fluid and leads to headache.

The headache which often follows lumbar puncture has predictable and unique features, all of which indicate its similarity to drainage headache. Like drainage headache, postpuncture headache was associated with a decrease in the volume of cerebrospinal fluid, as evidenced by a fall in cerebrospinal fluid pressure. It was completely eliminated by the intrathecal injection of saline solution and elevation of the intracranial pressure to normal. Its intensity was reduced by change from the erect to the horizontal position or by flexion or extension of the head, and its intensity was increased by bilateral jugular compression.

The usual postpuncture headache is, therefore, similar in type and mechanism to the headache induced by drainage of cerebrospinal fluid; i. e., it is caused by dilatation of and traction on pain-sensitive intracranial vascular structures. It is probably secondary to a prolonged leakage of fluid through the dural hole in the lumbar sac, produced by the operator's needle. Uncommonly postpuncture headache results from "sterile meningitis."

The headache so often associated with increased intracranial pressure has generally been assumed, but never proved, to be related to the increase in pressure. Yet elevation of intracranial pressure in normal human subjects to abnormally high levels failed to cause headache. Headache homolateral to the lesion in a patient with a cerebral tumor was induced by lowering the intracranial pressure but could not be induced by elevation of the pressure to 550 mm. Hence, in the production of headache, increased intracranial pressure is neither a prime nor an essential factor.

From these data, it is concluded that headache associated with either decreased or increased intracranial pressure results from traction on or displacement of pain-sensitive intracranial structures and is independent of generalized changes in intracranial pressure in themselves.

Headache Associated with Tumor of the Brain.—That increased intracranial pressure is not the dominant factor in headache associated with tumor of the brain was suggested by a study of 72 patients.

1. Headache occurred almost as commonly in 23 patients without increased intracranial pressure as it did in 49 patients with increased pressure (82 and 94 per cent respectively).

2. The reduction of elevated pressure did not inevitably eliminate headache associated with tumor.

3. At operation the headache could be reproduced experimentally by distortion of pain-sensitive structures adjacent to the tumor.

Headache associated with brain tumor is produced by traction on intracranial pain-sensitive structures, chiefly the large arteries, veins and venous sinuses, and certain cranial nerves. Two types of traction operate singly or in combination: local traction by the tumor on adjacent structures, and distant traction due to extensive displacement of the brain, either directly, by the tumor, or indirectly, by ventricular obstruction (internal hydrocephalus).

Headache as an aid in the localization of cerebral tumor is limited in its value by two facts: The headache may be remote from the site of its production, and the site of production of the headache may be remote from the tumor. In spite of these limitations, when the observations are interpreted in terms of known principles of production of intracranial pain and pain reference, the headache of brain tumor may significantly aid in the diagnosis and localization of the lesion.

Presentation of the following generalizations concerning the value of the headache associated with brain tumor as an aid to localization of the growth seems justified.

1. Although the headache of brain tumor is often referred from a distant intracranial source, the area of pain approximately overlies the tumor in about one third of all patients.

2. The presence of headache in the absence of papilledema in patients with brain tumor is of great localizing value. In about two thirds of the patients with such headache the area of pain immediately overlies, or is near, the tumor, and when it is unilateral it is always on the same side as the tumor.

3. Headache is almost always present with tumors of the posterior fossa.

4. Headache may be absent with any of the common types of supratentorial tumor.

5. The headache associated with tumors of the posterior fossa is almost always over the back of the head, although it may occur elsewhere.

6. Headache is usually the first symptom of tumors of the posterior fossa except for growths in the cerebellopontile angle.

7. Headache is the first symptom of one third of supratentorial tumors.

8. The headache of tumors of the cerebellopontile angle is frequently, and sometimes solely, postauricular.

9. Headache due to supratentorial tumors is rarely in the back of the head unless it is associated with papilledema.

10. When supratentorial tumor causes headache in the back of the head, headache in the front of the head is usually also present.

11. Headache which is both frontal and occipital indicates extensive displacement of the brain and has little localizing value.

12. The headache of brain tumor is usually intermittent, but when it is continuous its value in localization is greatly enhanced.

Histamine Headache.—The association of headache following intravenous injection of histamine with increase in the amplitude of the intracranial pulsations has been demonstrated. Simultaneous records of the systemic arterial blood pressure, the cerebrospinal fluid pressure, the pulsations of the temporal artery and the intracranial pulsations were made. The demonstrated correlation is taken as further evidence that the histamine headache is primarily due to dilation and stretching of the pial and dural arteries and their surrounding tissues.

Histamine headache was abolished by an increase in the intracranial pressure, extramural support being thus given to the cerebral arteries at the base of the brain. This is further evidence that histamine headache results chiefly from the dilatation and distention of cerebral arteries.

Histamine headache does not depend on the integrity of sensation from the superficial tissues. The extracranial and dural arteries play a minor role in contributing to the pain of histamine headache. Cerebral arteries, principally the large ones at the base of the brain, including the internal carotid, the vertebral and the basilar artery and the proximal segments of their main branches, are chiefly responsible for the quality and intensity of histamine headache. Although there may be other, less important, afferent pathways for the conduction of impulses interpreted as headache following injection of histamine, (*a*) the fifth cranial nerve on each side is the principal afferent pathway for headache resulting from dilatation of the supratentorial cerebral arteries and felt in the frontotemporoparietal region of the head, and (*b*) the ninth and tenth cranial and the upper cervical nerves are the most important afferent pathways for headache resulting from dilatation of the arteries of the posterior fossa and felt in the occipital region of the head.

Headache Associated with Fever.—Observations on the amplitude of pulsations of the cranial arteries during headache associated with experimentally induced fever showed that the spontaneous increase and decrease of intensity of the headache paralleled the changes in amplitude of pulsations in these arteries.

A similarity between the pyrexial and the histamine headache lay in the great increase in amplitude of pulsations of the cerebrospinal fluid in both types of headache, in contrast to migraine headache, which was not accompanied by any such increase. The observation was made, moreover, that an increase in the cerebrospinal fluid pressure in the subarachnoid space relieved headache associated with fever (Pickering).

The fact that increase in the intracranial pressure decreased the intensity of the headache indicates that the mechanism of the headache associated with fever and that of the headache following injection of histamine are similar and that, in both types, the intracranial arteries are the chief contributors to the pain. It is likely that the headaches associated with acute infection, sepsis and bacteremia are, similarly, due primarily to the distention of intracranial arteries.

Migraine Headache.—Changes in the intensity of migraine headache are related to changes in the amplitude of pulsations of the cranial arteries, chiefly the branches of the external carotid arteries. Factors which decrease the amplitude of pulsations decrease the intensity of the headache. Thus, it has also been shown by means of observations and photographs, made both before and during the action of ergotamine tartrate, that this agent reduces the amplitude of pulsations of the aforementioned arteries by about 50 per cent and thereby diminishes the intensity of or terminates the migraine headache. Reduction in the amplitude of pulsations of the temporal artery by digital pressure on the carotid artery on the affected side is accompanied by reduction in the intensity of the headache. The constriction of the branches of the external carotid artery, both superficial and dural, results in relief of migraine headache. Conversely, experimental distention of extracranial arteries by increase in the intravascular pressure results in pain.

Therefore, the headache of migraine is produced by distention of cranial arteries, chiefly, but not exclusively, the branches of the external carotid artery, and procedures that constrict the cranial arteries, and thus reduce their amplitude of pulsation, will diminish or terminate the headache.

The role of the pial and cerebral arteries in migraine headache needs further definition. It should be recalled that faradic stimulation of the proximal few centimeters of the anterior, middle and posterior cerebral arteries and the first few centimeters of the intracranial portion of the internal carotid artery causes pain within, behind or over the homolateral eye. Furthermore, stimulation of the vertebral and basilar arteries and the proximal portions of their branches causes pain in the occipital and suboccipital region. These areas are commonly involved in migraine attacks. The evidence from persons who have migraine headache that headache induced by histamine resembles the most intense migraine headache suggests that the larger arteries of the base of the brain and their immediate branches may be implicated in some patients during severe migraine headache.

On the other hand, there is considerable evidence against the view that the headache is due primarily to dilatation of the dural and cerebral arteries. If this were true, increase in the cerebrospinal fluid pressure, which dampens the pulsations of these vessels, would diminish the headache, as with the headache induced by histamine. The fact that not even some of the worst attacks of migraine headache are reduced in intensity by raising the cerebrospinal fluid pressure as high as 800 mm. of water by means of a manometer system attached to a needle in the lumbar sac indicates that the pial and cerebral arteries are not the major contributors to the pain.

The internal and external carotid arteries and the vertebral arteries have branches both in the subcutaneous tissue and in the meninges. The branches of the external carotid artery

predominate numerically, both superficially and on the dura. On the other hand, the anterior meningeal artery arises from branches of the internal carotid artery, as do the superficial frontal and the supraorbital artery. Since the area supplied by the latter structures is commonly involved in migraine headache branches of the internal carotid artery may contribute to the pain. It is obvious, therefore, that it would be arbitrary to differentiate between these arteries too sharply.

Although most attacks of migraine headache are limited to the temporal, the frontal or the occipital region, some patients have pain elsewhere. In the face, below the eye and behind and below the zygoma, severe, throbbing pain, which seems to emanate from the back teeth of the upper jaw, occasionally occurs. Another variant is facial pain, which spreads behind the angle of the jaw, down the neck and into the shoulder. The latter aching sensations are sometimes associated with awareness of unusual throbbing in the neck.

The pains described can, and probably do, result from dilatation and distention of the extracranial portion of the middle meningeal artery, between its origin and the point of entrance into the skull, the internal maxillary artery and the trunks of the external and the common carotid artery. It has been shown that the last-named structures are sensitive to pain, and the sites in which pain is felt are the face, neck and shoulder.

It is likely, therefore, that for histamine headache and the headache associated with fever, the cerebral branches of the internal carotid, basilar and vertebral arteries at the base of the brain are primarily responsible. To the migraine headache, however, the extracranial, and possibly the dural, branches of the external carotid artery are the chief contributors.

Mechanism of Scotomas Associated with Migraine Headache: To ascertain whether dysfunction of the cerebral vasculature is responsible for the preheadache symptom of scotoma, a vasodilator agent, amyl nitrite, known to affect cerebral vessels, was employed. It is justifiable to infer that cerebral vasodilatation induced without a fall in blood pressure increases cerebral blood flow, whereas a sharp drop in blood pressure, regardless of the state of the cerebral arteries, decreases cerebral blood flow. Symptoms due to cerebral vasoconstriction should be overcome by cerebral vasodilatation in the presence of a sustained normal level of blood pressure, but they should be augmented by a fall in blood pressure with accompanying decrease in cerebral blood flow. Experiments based on these two potential actions of the vasodilator drug amyl nitrite were performed by a subject having preheadache scotomas, who was skilful in observing his own visual fields. It was apparent from such experiments that cerebral vasodilatation associated with a sustained normal level of blood pressure caused the scotoma to disappear, whereas a procedure that decreased cerebral blood flow caused the symptom to become worse. From this it may be deduced that cerebral vasoconstriction was responsible for the visual defect in this patient with migraine. It is also likely that the cause of the visual defect was not in the retina or the orbit, but within the cranial cavity.

Pharmacodynamics of the Urine of Patients with Migraine: Under suitable laboratory circumstances, the urine of a healthy adult contracts the rectus abdominis muscle of the frog. Urine collected during the prodromal period of a migraine attack (period of scotoma) contracts the rectus abdominis muscle less than samples collected during attack-free periods, and urine collected during the headache contracts the muscle more. The 17-keto steroid content of the urine parallels this contraction-producing effect, as demonstrated by chemical determinations and biologic experiments. The gonadotropic principle of the hypophysis may contribute to this effect by itself or through increased liberation of androgen and estrogen. This increased ability, to produce muscular contraction, of the urine collected during an attack of migraine headache is probably not due to the potassium, acetylcholine, histamine or oxytocin content, nor is it related to the specific gravity of the urine. From the foregoing observations and from the fact that the aforementioned endocrine principles potentiate the effect of certain vasodilator substances, such as acetylcholine, it is conceivable that these substances participate in the production of the attack of migraine headache by potentiation of the effect of a local neurohumoral vasodilator agent.

Headache Associated with Hypertension.—Studies of the headache associated with hypertension have revealed that essentially the same mechanism is operative in producing this pain as in producing the migraine headache. It is to be emphasized that this statement applies not to the so-called hypertensive encephalopathy of Fishberg, or "hypertensive crisis," but, rather, to the frequent, severe and often incapacitating headache suffered by hypertensive patients who may otherwise be free of symptoms. The term "hypertensive headache" is misleading, since it implies that the frequency and severity of the headache are directly related to the level of the blood pressure.

Almost all the patients with hypertension and associated headache in this series had had headaches for many years. In many instances the headache was known to have preceded the

onset of the hypertension, and in some cases it changed only in intensity with the rise in blood pressure.

The following data indicate that the pial and cerebral arteries are not the prime contributors to the headache associated with hypertension, and that this headache, like that of migraine, arises chiefly from the dilatation and distention of certain branches of the external carotid artery: 1. The headache was not relieved by increase in the cerebrospinal fluid pressure. 2. There was no increase in the amplitude of pulsations of the intracranial arteries during the headache, and the amplitude of pulsations of these arteries did not become less as the headache diminished in intensity. 3. Ergotamine tartrate, which in the head acts chiefly on the branches of the external carotid artery, reduced the intensity of the headache. 4. Manual pressure on the temporal, frontal, supraorbital, postauricular or occipital artery decreased or abolished the headache. 5. Ligation of the middle meningeal or the temporal artery, especially the latter, decreased the intensity of the headache for some months.

That the headache in subjects with hypertension bears no direct relation to the level of blood pressure or pulse pressure has been previously observed. The headache may be present whether the blood pressure is relatively high, moderate or low. By pressure of the thumb on the common carotid artery the intensity of the headache is reduced, with an accompanying decline in the amplitude of the pulsation. Decrease in the intensity of headache in the temporal region followed similar pressure on the corresponding temporal artery. Furthermore, when ergotamine tartrate did succeed in appreciably decreasing the amplitude of pulsations of the cranial arteries for a shorter or longer period, intensity of the "hypertensive" headache decreased despite the fact that the ergotamine tartrate considerably increased the already elevated systolic and diastolic pressures. If little or no reduction of the amplitude of pulsation of the arteries occurred, there was no reduction in the intensity of the headache. Hence, headache associated with hypertension likewise is influenced by agents that decrease the amplitude of pulsations of the cranial arteries.

This view is illustrated further by the following case, which was studied intensively. A man with hypertension had incapacitating headaches every morning, chiefly on the right side. After an adequately long preliminary period of recording of the intensity and frequency, the right middle meningeal artery was ligated. After this procedure the daily headache on the side of operation was reduced to about one half or less of its former intensity. About a month later the right temporal artery, carefully avoided in the first operation, was ligated. This procedure was followed by almost complete freedom from headache on the right side. Less intense headaches, though present before, now became more troublesome over the left eye and temple. Hence, about a month later the left temporal artery was ligated. During the subsequent two months no headache was experienced in either the right or the left temporal region. Such headache as occurred, which was approximately one-third as intense as before, was now localized in the region immediately over both eyes and in the midline. Throughout these procedures the levels of systolic and diastolic blood pressure did not vary appreciably, and such changes as took place bore no direct relation to the intensity of the headache. These observations indicate the intimate relation of headache associated with hypertension and the cranial arteries.

The fact that the high level of blood pressure among hypertensive subjects is not a sufficient condition for headache does not justify the assumption that these phenomena are unrelated. Indeed, this, too, would be contradicted by the facts of common experience, since some persons with hypertension never had headache until the hypertension became established. It is reasonable to postulate that a cranial artery only slightly relaxed, for whatever reason, would not distend as much, and possibly not to the point of producing pain, if the blood pressure were low. If, however, the sustained level were raised, distention would be greater, and therefore pain might readily follow. In other words, a degree of change in the contractile state of the arterial wall, compatible with comfort when the blood pressure is average, is associated with pain when the blood pressure is elevated.

This conception is supported by analogy with experimental evidence on histamine headache. The headache and maximal distention of the cranial arteries occur not immediately after the injection of histamine, when the effect on the contractile state of these vessels is greatest, but some time later, when the blood pressure returns to its initial level. It is at this time that the walls of the cranial artery react to the mounting pressure and headache becomes associated with a level of blood pressure which is ordinarily associated with comfort. The relaxation of arterial walls is thus seen to be one necessary factor in the production of histamine headache, and the level of the blood pressure, the other. The analogy to the circumstances associated with hypertension is close. During an average or a normal contractile state of the arterial walls, distention does not occur and, correspondingly, there is no headache, but should this contractile state be impaired, as by stress or fatigue, distention and headache follow. In brief,

high blood pressure is a necessary, but not sufficient, condition for this type of headache. There is a significant relation between headache associated with hypertension and the contractile state of the cranial arteries.

Relation of Headache to the Eyes.—The association of headache with various ocular disorders has long been recognized as a clinical entity. Of the organic disorders, errors of refraction (hypermetropia, astigmatism and anomalies of accommodation), disturbances of muscular equilibrium and glaucoma are universally described as causing headache. Refractive errors are said, in addition, to give origin to such symptoms as aching of the eyes, a feeling of sand in the eyes, pulling sensations in and about the orbit and congestion of the conjunctiva. Investigations have been made on the pain-sensitive structures, both superficial and deep, of the eye, on the headache and aching of the eyes associated with refractive errors and imbalances of the extraocular muscles and on photophobia.

With persons having normal eyes, the modalities of touch, pain and temperature sense were studied in both the conjunctiva and the cornea. Wisps of cotton applied to the conjunctiva produced the sensation of touch without pain, and localization of the area touched was fairly accurate. Applicators cooled to below 30 C. were recognized as cool or cold, whereas those above this temperature up to 70 C., produced only touch sensation. Sharp stimuli and pinching produced pain. On the cornea only pain and cold sensations were recognized.

Patients with increased intraocular pressure described a sharp pain which at first remained localized in the eyeball, then extended as a "bad ache" along the rim of the orbit and finally involved most of the area supplied by the ophthalmic division of the trigeminal nerve. Nausea and vomiting sometimes accompanied such headache. During operation for strabismus with local anesthesia pinching, sticking or cutting of the rectus muscles caused no sensation, but traction produced prompt exclamations of pain. The pain was described as an aching sensation felt in the eye on the same side as the muscle stimulated, and deep in the orbit. There was no consistent radiation of pain from traction on the rectus muscle, and no pain was felt in the back of the head or in the neck.

Traction on the tissue of the iris with a small-toothed forceps or traction produced by chemical agents (mydriatics or miotics) caused varying degrees of pain in the eyeball, which in some instances was accompanied by radiation to the area supplied by the ophthalmic division of the trigeminal nerve on the same side.

It is recognized that hyperopia, astigmatism and pronounced imbalance of the extraocular muscles may produce such symptoms as ocular discomfort and aching, a feeling of heaviness in the head and actual headache, which usually starts around and over the eyes and subsequently radiates to the occiput and to the back of the head. Furthermore, it was found that experimentally induced hyperopia and astigmatism caused headache, while induced myopia did not. Induced imbalance of the extraocular muscles caused tension and irritability, and if it was prolonged, headache developed, with abnormal electromyograms from the muscles of the scalp and neck. Normally occurring muscle imbalances produce similar symptoms and myograms.

Photophobia may be of two varieties. In the diseased eye, in which inflammation of the iris and the ciliary body exists, light may cause intense pain, felt in the eye and over the area supplied by the ophthalmic division of the fifth nerve, when the light stimulus is accompanied by movement of the inflamed iris. When the iris is immobilized, pain is allayed. It is obvious, therefore, that this type of photophobia results from direct mechanical trauma of the light reflex on the iris.

Another type of photophobia occurs in persons with healthy irises. It can be elicited by abnormally large amounts of light or by normal amounts of light under certain conditions, such as surface irritation of the conjunctiva by chemical (2 per cent ethylmorphine hydrochloride) or mechanical (foreign body) means. Vascular congestion can be abolished without such experimentally induced photophobia being affected, while, on the other hand, it can be relieved by surface anesthesia, but not by mydriasis or cycloplegia. Surface anesthesia also reduces the normal winking response to a bright light. This is probably due to abolition of the normal sensory impulses from air currents, lid pressure, etc.

Photophobia is caused by ophthalmic irritation plus stimulation with light. It does not occur in the presence of the Argyll Robertson pupil.

Muscles of the Scalp and Neck as Sources of Pain.—The effect of pain in the head on the muscles of the scalp and neck was studied in nine series of experiments. Muscle potentials were recorded on a two channel ink-writing oscillograph by means of solder electrodes applied over the frontal, temporal and cervical muscles.

In one series of experiments pain in the head of short duration was induced by the intravenous injection of histamine. Contraction of the muscles of the scalp and neck was observed in

association with the pain, but no pain appeared in the muscles themselves, probably because of the short duration of the induced pain in the head.

In a second series of observations on the effect of headache associated with spinal drainage on the muscles of the scalp and neck, strong muscular contraction in the frontal and parietal areas followed the onset of frontal headache, but in these short experiments no secondary pain occurred.

In another series pain was prolonged in the head by means of successive injections of a 6 per cent solution of sodium chloride into the right temporal muscle. This continuous pain in the head caused pronounced muscular contraction and secondary pain in the neck.

In a fourth series of experiments an irritant introduced into the conjunctival sac caused contraction of the muscles of the scalp and neck and gave rise to secondary pain and paresthesia in the scalp and neck.

Abnormally sustained contraction of the extraocular muscles, brought about by a vertical prism of 3 prism diopters placed in front of the dominant eye, caused sustained contraction of the muscles of the neck, followed by pain in the neck and shoulder on the same side.

In subjects suffering from inflammation or other disorders about the head (pansinusitis, migraine or emotional tension) there was sustained contraction of the muscles of the neck or scalp, with concomitant pain in the neck and over the back of the head.

These studies demonstrate that noxious stimulation of the head or emotional tension leads to sustained contraction of the muscles of the scalp and neck. This muscular tension may give rise to painful sensations in the shoulders, neck and head. The mechanism of this pain is sustained muscular contraction.

Pain Associated with Disease of the Nasal and Paranasal Structures—The "Sinus Headache."—The headache associated with disease of the frontal sinus was localized diffusely over the frontal region, and the headache associated with antral disease, over the maxillary region. The headache associated with disease of the sphenoid and ethmoid sinuses was experienced between and back of the eyes and over the vertex. Commonly, when sinus disease was of sufficient duration, there was pain in the back of the head, neck and shoulders, in addition to the headache experienced in the front and the top of the head.

Headache was less frequent when the patient had been lying down or resting for some time and was less often present at night than during the day. Moreover, the pain associated with disease of the maxillary sinus gradually diminished when the patient assumed the recumbent position with the diseased side uppermost. This relief was not prompt, usually requiring about thirty minutes.

The headache associated with disease of the frontal sinus commonly began about 9 a. m., gradually became worse and ended toward evening or on the patient's retiring to bed. The pain associated with disease of the maxillary sinus usually had its onset in the early afternoon.

The pain referable to any of the sinuses was of a deep, dull, aching, nonpulsatile quality. It was seldom, if ever, associated with vomiting or nausea. The headache which accompanied chronic sinus disease was of a low order of intensity. The headache associated with acute sinus disease was sometimes of greater intensity, but was seldom very severe. Pain did not achieve the intensity noted in some cases of migraine or the severity of the headache associated with rupture of a cerebral aneurysm, meningitis or certain febrile illnesses or of that induced by certain drugs.

The headache associated with disease of the nasal and paranasal structures was commonly reduced in intensity or abolished by acetylsalicylic acid or codeine. The intensity of pain was increased by the subject's shaking the head or his assuming the head-down position. The headache was intensified by factors which increased the venous pressure, such as straining, coughing or the wearing of a tight collar. Also, it was intensified by states that increased the engorgement of the mucosa, such as anxiety and resentment, menstruation, cold air, sexual excitement or the effects of alcohol.

The mucosa covering the approaches to the paranasal sinuses was found to be the most sensitive to pain of the nasal and paranasal structures and cavities, whereas the mucosa lining the sinuses was of relatively low sensitivity. A given faradic stimulus to the tongue which elicited pain of 1 + intensity when applied to the septum was experienced as pain of about 1 + to 2 + intensity; when applied to the turbinates, as pain of 4 + to 6 + intensity; when applied to the nasofrontal duct, as pain of 5 + to 7 + intensity; when applied to the ostium, as pain of 6 + to 9 + intensity, and when applied to the lining of the frontal or the maxillary sinus, as pain of 1 + to 2 + intensity.

Most of the pain arising from faradic, mechanical and chemical stimulation of the mucosa of the nasal and paranasal cavities was referred; i. e., it was felt at a site other than that stimulated. It was diffuse, sustained, of a deep, aching nature and nonpulsatile. It was associated

with lacrimation, photophobia, erythema and hyperalgesia. The pain and its associated effects outlasted the period of stimulation.

The pain thus induced experimentally was referred chiefly to the regions of the head supplied by the second division, and to a less extent to those supplied by the first division, of the fifth cranial nerve. When it was severe enough, or of sufficient duration, the pain spread over most of the region supplied by the division of the fifth cranial nerve to which it was initially referred, and sometimes spread from the region of the second to that of the first division.

Stimulation of several sites resulted in pain referred to the same region. Thus, stimulation of the nasal structures near the midline resulted in pain referred to the same area as did stimulation of the ostium and the more lateral wall of the maxillary sinus.

Pain in the back of the head or neck never resulted directly from stimulation of the mucosa of any of the nasal or paranasal structures. Such pain was due to the secondary effects of prolonged contraction of the muscles of the neck and scalp.

Section of the sensory root of the fifth cranial nerve in most instances caused the mucosa of the aforementioned spaces to be insensitive, except for the pharynx, the tonsils, the fossa of Rosenmüller, the eustachian tubes, the external auditory canal and the ear drum.

Inflammation and engorgement of the turbinates, ostiums, nasofrontal ducts and superior nasal spaces are responsible for most of the pain emanating from the nasal and paranasal structures. If a headache is not associated with engorgement and inflammation of the turbinates, it is in all probability not the result of disease of the nasal or paranasal structures. Furthermore, if headache in the zygomatic, frontal or temporal regions or over the vertex is not greatly reduced in intensity or eliminated by shrinkage or local anesthetization of the nasal structures, it also is, in all probability not due to disease of the nasal or paranasal structures.

News and Comment

ILLINOIS PSYCHIATRIC SOCIETY

At the annual meeting of the Illinois Psychiatric Society, held in Chicago May 22, the following officers were elected for the year 1943-1944: Dr. Clarence A. Neymann, president; Dr. Hugh T. Carmichael, vice president; Dr. Frances Hannett, secretary-treasurer, and Dr. Francis J. Gerty and Dr. Vladimir Urse, councilors.